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DPP-IV inhibitors

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DPP-IV inhibitors

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The present invention relates to a novel class of dipeptidyl peptidase inhibitors, including pharmaceutically acceptable salts and prodrugs thereof, which are useful as therapeutic compounds, particularly in the treatment of Type 2 diabetes mellitus, often referred to as non-insulin dependent diabetes mellitus (NIDDM), and of conditions that are often associated with this disease, such as obesity and lipid disorders.

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Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at an increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutic control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

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There are two generally recognized forms of diabetes. In Type 1, or insulin-dependent, diabetes mellitus (IDDM), patients produce little or no insulin, which is the hormone regulating glucose utilization. In Type 2, or noninsulin dependent, diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or elevated compared to nondiabetic subjects. These patients develop a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, namely the muscle, liver and adipose tissues. Further, the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

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Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle, and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

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The available treatments for Type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g., tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β -cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance, due to the even higher plasma insulin levels, can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhoea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

The glitazones (*i.e.*, 5-benzylthiazolidine-2,4-diones) are a recently described class of compounds with potential for ameliorating many symptoms of Type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of Type 2 diabetes, resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type 2 diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (*i.e.*, they are not thiazolidinediones). Serious side effects (*e.g.*, liver toxicity) have occurred with some of the glitazones, such as troglitazone.

Additional methods of treating the disease are still under investigation. New biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (*e.g.*, acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

Compounds that are inhibitors of the dipeptidyl peptidase-IV (DPP-IV) enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly Type 2 diabetes. See for example WO-A-97/40832, WO-A-98/19998,

WO-A-03/180 and WO-A-03/181. The usefulness of DPP-IV inhibitors in the treatment of Type 2 diabetes is based on the fact that DPP-IV *in vivo* readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are incretins and are produced when food is consumed. The incretins stimulate production of insulin. Inhibition of DPP-IV leads to decreased inactivation of the incretins, and this in turn results in increased effectiveness of the incretins in stimulating production of insulin by the pancreas. DPP-IV inhibition therefore results in an increased level of serum insulin. Advantageously, since the incretins are produced by the body only when food is consumed, DPP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DPP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect associated with the use of insulin secretagogues.

DPP-IV inhibitors may also have other therapeutic utilities, as discussed elsewhere in this application. DPP-IV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DPP-IV inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions.

Thus, the object of the present invention is to provide a new class of DPP-IV inhibitors which may be effective in the treatment of Type 2 diabetes and other DPP-IV modulated diseases.

Accordingly, the present invention provides novel compounds of formula (I):



or a pharmaceutically acceptable salt thereof, wherein

Z is selected from the group consisting of phenyl; naphthyl; indenyl; C₃₋₇ cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R⁸, wherein R⁸ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; R⁹; and R¹⁰;

R^9 is selected from the group consisting of C_{1-6} alkyl; $O-C_{1-6}$ alkyl; and $S-C_{1-6}$ alkyl, wherein R^9 is optionally interrupted by oxygen and wherein R^9 is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

- 5 R^{10} is selected from the group consisting of phenyl; heterocycle; and C_{3-7} cycloalkyl, wherein R^{10} is optionally substituted with one or more R^{11} , wherein R^{11} is independently selected from the group consisting of halogen; CN; OH; NH_2 ; oxo ($=O$), where the ring is at least partially saturated; C_{1-6} alkyl; $O-C_{1-6}$ alkyl; and $S-C_{1-6}$ alkyl;

- 10 R^1, R^4 are independently selected from the group consisting of H; F; OH; and R^{4a} ;

R^2, R^5 are independently selected from the group consisting of H; F; and R^{4b} ;

- 15 R^{4a} is independently selected from the group consisting of C_{1-6} alkyl; and $O-C_{1-6}$ alkyl, wherein R^{4a} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{4b} is C_{1-6} alkyl, wherein R^{4b} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

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R^3 is selected from the group consisting of H; and C_{1-6} alkyl;

- 25 Optionally one or more pairs of R^1, R^2, R^3, R^4, R^5 independently selected from the group consisting of R^1/R^2 ; R^2/R^3 ; R^3/R^4 ; and R^4/R^5 form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more of R^{12} , wherein R^{12} is independently selected from the group consisting of F; Cl; and OH;

X is selected from the group consisting of S(O); $S(O)_2$; C(O); and $C(R^{13}R^{14})$;

- 30 R^{13}, R^{14} are independently selected from the group consisting of H; F; C_{1-6} alkyl; R^{15} ; and R^{16} ;

- 35 Optionally one or both pairs of R^5, R^{13}, R^{14} selected from the group consisting of R^5/R^{13} ; and R^{13}/R^{14} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{17} , wherein R^{17} is independently selected from the group consisting of F; Cl; and OH;

R^{15} is selected from the group consisting of phenyl; naphthyl; and indenyl, wherein R^{15} is optionally substituted with one or more R^{18} , wherein R^{18} is independently selected from the

group consisting of R^{19} ; R^{20} ; halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{21})$ - C_{1-6} alkyl; $S(O)_2N(R^{21})$ - C_{1-6} alkyl; $S(O)N(R^{21})$ - C_{1-6} alkyl; $S(O)_2$ - C_{1-6} alkyl; $S(O)$ - C_{1-6} alkyl; $N(R^{21})S(O)_2$ - C_{1-6} alkyl; and $N(R^{21})S(O)$ - C_{1-6} alkyl, wherein each

5 C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{16} is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tertralinyl; and decaliny, wherein R^{16} is optionally substituted with

10 one or more R^{22} , wherein R^{22} is independently selected from the group consisting of R^{19} ; R^{20} ; halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2 ; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; $N(R^{23})$ - C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{23})$ - C_{1-6} alkyl; $N(R^{23})$ - $C(O)$ - C_{1-6} alkyl; $S(O)_2N(R^{23})$ - C_{1-6} alkyl; $S(O)N(R^{23})$ - C_{1-6} alkyl; $S(O)_2$ - C_{1-6} alkyl; $S(O)$ - C_{1-6} alkyl;

15 $N(R^{23})S(O)_2$ - C_{1-6} alkyl; and $N(R^{23})S(O)$ - C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{19} is selected from the group consisting of phenyl; and naphthyl, wherein R^{19} is optionally

20 substituted with one or more R^{24} , wherein R^{24} is independently selected from the group consisting of halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{25})$ - C_{1-6} alkyl; $S(O)_2N(R^{25})$ - C_{1-6} alkyl; $S(O)N(R^{25})$ - C_{1-6} alkyl; $S(O)_2$ - C_{1-6} alkyl; $S(O)$ - C_{1-6} alkyl; $N(R^{25})S(O)_2$ - C_{1-6} alkyl; and $N(R^{25})S(O)$ - C_{1-6} alkyl, wherein each

25 C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{20} is selected from the group consisting of heterocycle; heterobicycle; and C_{3-7} cycloalkyl; wherein R^{20} is optionally substituted with one or more R^{26} , wherein R^{26} is

30 independently selected from the group consisting of halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2 ; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; $N(R^{27})$ - C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{27})$ - C_{1-6} alkyl; $N(R^{27})$ - $C(O)$ - C_{1-6} alkyl; $S(O)_2N(R^{27})$ - C_{1-6} alkyl; $S(O)N(R^{27})$ - C_{1-6} alkyl; $S(O)_2$ - C_{1-6} alkyl; $S(O)$ - C_{1-6} alkyl; $N(R^{27})S(O)_2$ - C_{1-6} alkyl; and

35 $N(R^{27})S(O)$ - C_{1-6} alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

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R^{21} , R^{23} , R^{25} , R^{27} are independently selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more of R^{28} , wherein R^{28} is independently selected from the group consisting of F; Cl and OH;

5 R^6 , R^7 are independently selected from the group consisting of H; $(C(R^{29}R^{30}))_m-X^1-Z^1$; and $(C(R^{31}R^{32}))_n-X^2-X^3-Z^2$, provided that R^6 , R^7 are selected so that not both of R^6 , R^7 are independently selected from the group consisting of H; CH_3 ; CH_2CH_3 ; $CH_2CH_2CH_3$; and $CH(CH_3)_2$;

10 Optionally R^6 , R^7 are independently C_{1-4} alkyl, which is substituted with one or more R^{29a} , wherein R^{29a} is independently selected from the group consisting of R^{29b} ; and Z^1 , provided that R^6 , R^7 are selected so that not both of R^6 , R^7 are independently selected from the group consisting of CH_3 ; CH_2CH_3 ; $CH_2CH_2CH_3$; and $CH(CH_3)_2$;

15 R^{29} , R^{29b} , R^{30} , R^{31} , R^{32} are independently selected from the group consisting of H; halogen; CN; OH; NH_2 ; $COOH$; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; $N(R^{32a})-C_{1-6}$ alkyl; $COO-C_{1-6}$ alkyl; $OC(O)-C_{1-6}$ alkyl; $C(O)N(R^{32a})-C_{1-6}$ alkyl; $N(R^{32a})-C(O)-C_{1-6}$ alkyl; $S(O)_2N(R^{32a})-C_{1-6}$ alkyl; $S(O)N(R^{32a})-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $N(R^{32a})S(O)_2-C_{1-6}$ alkyl; and $N(R^{32a})S(O)-C_{1-6}$ alkyl wherein each

20 C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{32a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F;

25 and Cl;

Optionally one or more pairs of R^{29} , R^{30} , R^{31} , R^{32} independently selected from the group consisting of R^{29}/R^{30} ; and R^{31}/R^{32} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{32b} , wherein R^{32b} is independently selected from the group

30 consisting of F; Cl; and OH;

m is 0, 1, 2, 3 or 4;

n is 2, 3 or 4;

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X^1 is independently selected from the group consisting of a covalent bond; $-C_{1-6}$ alkyl-; $-C_{1-6}$ alkyl-O-; $-C_{1-6}$ alkyl- $N(R^{33})$ -; $-C(O)$ -; $-C(O)-C_{1-6}$ alkyl-; $-C(O)-C_{1-6}$ alkyl-O-; $-C(O)-C_{1-6}$ alkyl- $N(R^{33})$ -; $-C(O)O$ -; $-C(O)O-C_{1-6}$ alkyl-;

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- 5 $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl-O-; $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{33})$ -; $-\text{C}(\text{O})\text{N}(\text{R}^{33})$ -; $-\text{C}(\text{O})\text{N}(\text{R}^{33})-\text{C}_{1-6}$ alkyl-; $-\text{C}(\text{O})\text{N}(\text{R}^{33})-\text{C}_{1-6}$ alkyl-O-; $-\text{C}(\text{O})\text{N}(\text{R}^{33})-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{34})$ -; $-\text{S}(\text{O})_2$ -; $-\text{S}(\text{O})$ -; $-\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl-; $-\text{S}(\text{O})-\text{C}_{1-6}$ alkyl-; $-\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl-O-; $-\text{S}(\text{O})-\text{C}_{1-6}$ alkyl-O-; $-\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{33})$ -; and $-\text{S}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{33})$ -; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

X^2 is selected from the group consisting of -O-; -S-; -S(O)-; $\text{S}(\text{O})_2$ -; and - $\text{N}(\text{R}^{35})$ -;

- 10 X^3 is selected from the group consisting of a covalent bond; $-\text{C}_{1-6}$ alkyl-; $-\text{C}_{1-6}$ alkyl-O-; $-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{36})$ -; $-\text{C}(\text{O})$ -; $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl-; $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl-O-; $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{36})$ -; $-\text{C}(\text{O})\text{O}$ -; $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl-; $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl-O-; $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{36})$ -; $-\text{C}(\text{O})\text{N}(\text{R}^{36})$ -; $-\text{C}(\text{O})\text{N}(\text{R}^{36})-\text{C}_{1-6}$ alkyl-; $-\text{C}(\text{O})\text{N}(\text{R}^{36})-\text{C}_{1-6}$ alkyl-O-; and $-\text{C}(\text{O})\text{N}(\text{R}^{36})-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{37})$ -; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

- Optionally X^2 - X^3 are independently selected from the group consisting of - $\text{N}(\text{R}^{35})$ - $\text{S}(\text{O})_2$ -; - $\text{N}(\text{R}^{35})$ - $\text{S}(\text{O})$ -; - $\text{N}(\text{R}^{35})$ - $\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl-; - $\text{N}(\text{R}^{35})$ - $\text{S}(\text{O})-\text{C}_{1-6}$ alkyl-; - $\text{N}(\text{R}^{35})$ - $\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl-O-; - $\text{N}(\text{R}^{35})$ - $\text{S}(\text{O})-\text{C}_{1-6}$ alkyl-O-; - $\text{N}(\text{R}^{35})$ - $\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{36})$ -; and - $\text{N}(\text{R}^{35})$ - $\text{S}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{36})$ -; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

- 25 R^{33} , R^{34} , R^{35} , R^{36} , R^{37} are independently selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Z^1 , Z^2 are independently selected from the group consisting of Z^3 ; and $-\text{C}(\text{R}^{37a})\text{Z}^{3a}\text{Z}^{3b}$;

- 30 R^{37a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more F;

- 35 Z^3 , Z^{3a} , Z^{3b} are independently selected from the group consisting of H; T^1 ; T^2 ; C_{1-6} alkyl; C_{1-6} alkyl- T^1 ; and C_{1-6} alkyl- T^2 ; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{37b} , wherein R^{37b} is independently selected from the group consisting of halogen; CN; OH; NH_2 ; COOH; $\text{C}(\text{O})\text{NH}_2$; $\text{S}(\text{O})_2\text{NH}_2$; $\text{S}(\text{O})\text{NH}_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; $\text{N}(\text{R}^{37c})-\text{C}_{1-6}$ alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $\text{C}(\text{O})\text{N}(\text{R}^{37c})-\text{C}_{1-6}$ alkyl; $\text{N}(\text{R}^{37c})-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl; $\text{S}(\text{O})_2\text{N}(\text{R}^{37c})-\text{C}_{1-6}$ alkyl; $\text{S}(\text{O})\text{N}(\text{R}^{37c})-\text{C}_{1-6}$ alkyl; $\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl; $\text{S}(\text{O})-\text{C}_{1-6}$ alkyl; $\text{N}(\text{R}^{37c})\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl; and $\text{N}(\text{R}^{37c})\text{S}(\text{O})-\text{C}_{1-6}$ alkyl; wherein each

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C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

5 T¹ is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T¹ is optionally substituted with one or more R³⁸; wherein R³⁸ is independently selected from the group consisting of halogen; CN; R³⁹; COOH; OH; C(O)NH₂; S(O)₂NH₂; S(O)NH₂; COOT³; OT³; ST³; C(O)N(R⁴⁰)T³; S(O)₂N(R⁴⁰)T³; S(O)N(R⁴⁰)T³ and T³;

10 T² is selected from the group consisting of C₃₋₇ cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein T² is optionally substituted with one or more R⁴¹, wherein R⁴¹ is independently selected from the group consisting of halogen; CN; R⁴²; OH; oxo (=O), where the ring is at least partially saturated; NH₂; COOH; C(O)NH₂; S(O)₂NH₂; S(O)NH₂; COOT³; OT³; C(O)N(R⁴³)T³; S(O)₂N(R⁴³)T³; S(O)N(R⁴³)T³; N(R⁴³)T³; and T³;

15 R³⁹ is selected from the group consisting of C₁₋₆ alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R⁴⁴)-C₁₋₆ alkyl; S(O)₂N(R⁴⁴)-C₁₋₆ alkyl; S(O)N(R⁴⁴)-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; N(R⁴⁴)S(O)₂-C₁₋₆ alkyl; and N(R⁴⁴)S(O)-C₁₋₆ alkyl; wherein each C₁₋₆ alkyl is optionally substituted with one or more R⁴⁵,
20 wherein R⁴⁵ is independently selected from the group consisting of F; COOR⁴⁶; C(O)N(R⁴⁶R⁴⁷); S(O)₂N(R⁴⁶R⁴⁷); OR⁴⁶; N(R⁴⁶R⁴⁷); T³; O-T³; and N(R⁴⁶)-T³;

R⁴² is selected from the group consisting of C₁₋₆ alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; N(R⁴⁸)-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R⁴⁸)-C₁₋₆ alkyl; N(R⁴⁸)-C(O)-C₁₋₆ alkyl; S(O)₂N(R⁴⁸)-C₁₋₆ alkyl; S(O)N(R⁴⁸)-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; -N(R⁴⁸)S(O)₂-C₁₋₆ alkyl; and -N(R⁴⁸)S(O)-C₁₋₆ alkyl; wherein each C₁₋₆ alkyl is optionally substituted with one or more R⁴⁵, wherein R⁴⁵ is independently selected from the group consisting of F; COOR⁴⁹; C(O)N(R⁴⁹R⁵⁰); S(O)₂N(R⁴⁹R⁵⁰); S(O)N(R⁴⁹R⁵⁰); OR⁴⁹; N(R⁴⁹R⁵⁰); T³; O-T³; and N(R⁴⁹)-T³;

30 R⁴⁰, R⁴³, R⁴⁴, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰ are independently selected from the group consisting of H; and C₁₋₆ alkyl;

T³ is selected from the group consisting of T⁴; and T⁵;

35 T⁴ is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T⁴ is optionally substituted with one or more R⁵¹, wherein R⁵¹ is independently selected from the group consisting of halogen; CN; COOR⁵²; OR⁵²; C(O)N(R⁵²R⁵³); S(O)₂N(R⁵²R⁵³); C₁₋₆

alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R⁵²)-C₁₋₆ alkyl; S(O)₂N(R⁵²)-C₁₋₆ alkyl; S(O)N(R⁵²)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; N(R⁵²)S(O)₂-C₁₋₆ alkyl; and N(R⁵²)S(O)-C₁₋₆ alkyl; wherein each C₁₋₆ alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

T⁵ is selected from the group consisting of heterocycle; heterobicycle; C₃₋₇ cycloalkyl; indanyl; tetralinyl; and decalinyl; wherein T⁵ is optionally substituted with one or more R⁵⁴, wherein R⁵⁴ is independently selected from the group consisting of halogen; CN; OR⁵⁵; oxo (=O), where the ring is at least partially saturated; N(R⁵⁵R⁵⁶); COOR⁵⁵; C(O)N(R⁵⁵R⁵⁶); S(O)₂N(R⁵⁵R⁵⁶); S(O)N(R⁵⁵R⁵⁶); C₁₋₆ alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; N(R⁵⁵)-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R⁵⁵)-C₁₋₆ alkyl; N(R⁵⁵)-C(O)-C₁₋₆ alkyl; S(O)₂N(R⁵⁵)-C₁₋₆ alkyl; S(O)N(R⁵⁵)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; N(R⁵⁵)S(O)₂-C₁₋₆ alkyl; and N(R⁵⁵)S(O)-C₁₋₆ alkyl; wherein each C₁₋₆ alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

R⁵², R⁵³, R⁵⁵, R⁵⁶, are independently selected from the group consisting of H; and C₁₋₆ alkyl.

Within the meaning of the present invention the terms are used as follows:

In case a variable or substituent can be selected from a group of different variants and such variable or substituent occurs more than once the respective variants can be the same or different.

"Alkyl" means a straight-chain or branched carbon chain that may contain double or triple bonds. It is generally preferred that alkyl doesn't contain double or triple bonds.

"C₁₋₄ Alkyl" means an alkyl chain having 1 - 4 carbon atoms, e.g. at the end of a molecule methyl, ethyl, -CH=CH₂, -C≡CH, n-propyl, isopropyl, -CH=CH-CH₃, -CH₂-CH=CH₂, n-butyl, isobutyl, -CH=CH-CH₂-CH₃, -CH=CH-CH=CH₂, sec-butyl tert-butyl or amid, e.g. -CH₂-, -CH₂-CH₂-, -CH=CH-, -CH(CH₃)-, -C(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)-, -CH(CH₃)₂-.

"C₁₋₆ Alkyl" means an alkyl chain having 1 - 6 carbon atoms, e.g. C₁₋₄ alkyl, methyl, ethyl, -CH=CH₂, -C≡CH, n-propyl, isopropyl, -CH=CH-CH₃, -CH₂-CH=CH₂, n-butyl, isobutyl, -CH=CH-CH₂-CH₃, -CH=CH-CH=CH₂, sec-butyl tert-butyl, n-pentane, n-hexane, or amid, e.g. -CH₂-, -CH₂-CH₂-, -CH=CH-, -CH(CH₃)-, -C(CH₃)-,

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$-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{C}_2\text{H}_5)-$, $-\text{CH}(\text{CH}_3)_2-$. Each hydrogen of a C_{1-6} alkyl carbon may be replaced by a substituent.

5 "C₃₋₇ Cycloalkyl" or "C₃₋₇ Cycloalkyl ring" means a cyclic alkyl chain having 3 - 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent.

"Halogen" means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

10

"Heterocycle" means a cyclopentane, cyclohexane or cycloheptane ring that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one carbon atom up to 4 carbon atoms are replaced by a heteroatom selected from the group consisting of sulfur (including $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$), oxygen and nitrogen (including $=\text{N}(\text{O})-$) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a heterocycle are furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine,

15

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pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, azepine or homopiperazine.

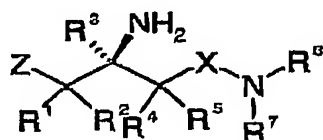
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"Heterobicycle" means a heterocycle which is condensed with phenyl or an additional heterocycle to form a bicyclic ring system. "Condensed" to form a bicyclic ring means that two rings are attached to each other by sharing two ring atoms. Examples for a heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, dihydroquinoline, isoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine or pteridine.

30

A preferred stereochemistry of compounds or a pharmaceutically acceptable salt thereof according to the present invention is shown in formula (Ia)

35



(Ia)

wherein Z, R¹-R⁷ and X have the meaning as indicated above.

5 Preferred compounds of formula (I) or (Ia) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formulas (I) or (Ia) the present invention also includes all tautomeric and stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

10 In preferred embodiments of the present invention, the substituents Z, R¹-R⁷ and X of the formula (I) or (Ia) independently from each other have the following meaning. Hence, one or more of the substituents Z, R¹-R⁷ and X can have the preferred or more preferred meanings given below.

15 Preferably, Z is phenyl or heterocycle.

Preferably, Z is optionally substituted with 1 or 2 R⁸, which are the same or different.

20 Preferably, R⁸ is selected from the group consisting of Cl; F; CN; CH₃; and OCH₃.

In a more preferred embodiment Z is 2-Fluoro-phenyl.

25 Preferably, R¹, R⁴ are independently selected from the group consisting of H; F; OH; CH₃; and OCH₃.

Preferably, R², R⁵ are independently selected from the group consisting of H; F; and CH₃.

R¹, R², R⁴, R⁵ are more preferred H.

30 Preferably, R³ is H.

Preferably, X is C(O).

35 R⁶ is preferably selected from the group consisting of H; and CH₃.

Preferably, X¹ is a covalent bond.

Preferably, m is 0, 1, 2 or 3.

Preferably, R^7 is Z^1 .

Preferably, R^7 is C_{1-4} alkyl, substituted with 1-4 R^{29a} , which are the same or different.

5

R^7 is more preferred selected from the group consisting of $CH(R^{29a})_2$; $CHR^{29a}-CH_2R^{29a}$; $CH_2-CH(R^{29a})_2$; $CH_2-CHR^{29a}-CH_2R^{29a}$; and $CH_2-CH_2-CH(R^{29a})_2$.

Preferably, R^{29a} is selected from the group consisting of R^{29b} ; and Z^1 ; wherein R^{29b} is selected from the group consisting of H; F; Cl; NH_2 ; $NHCH_3$; $N(CH_3)_2$; CH_3 ; and C_2H_5 .

10

Preferably, R^{29a} is selected from the group consisting of R^{29b} ; and Z^1 ; wherein Z^1 is selected from the group consisting of T^1 ; and T^2 .

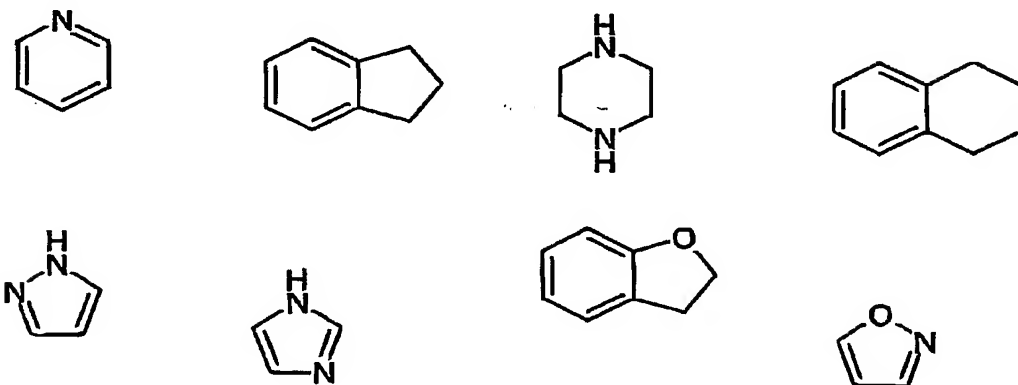
Preferably, T^1 is phenyl; wherein T^1 is optionally substituted with 1-3 R^{38} , which are the same or different.

15

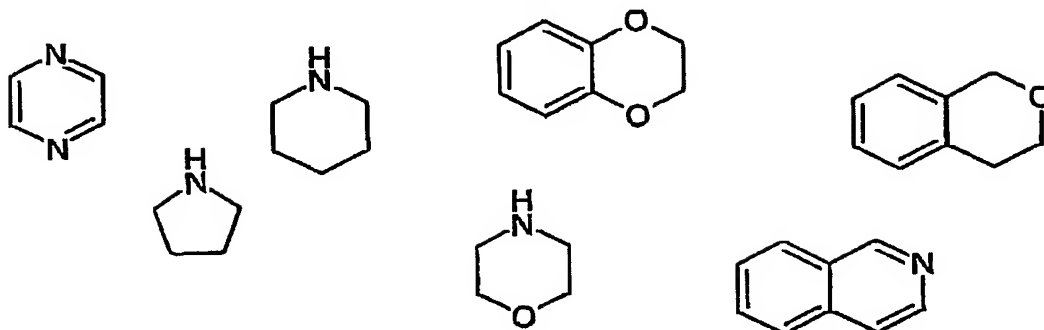
Preferably, R^{38} is independently selected from the group consisting of F; Cl; CN; CH_3 ; C_2H_5 ; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3 ; $O-CH_3$; $O-C_2H_5$; $S-CH_3$; SO_2NH_2 ; T^3 ; and $O-T^3$.

20

Preferably, T^2 is selected from the group consisting of



- 13 -



wherein T^2 is optionally substituted with 1-2 R^{41} , which are the same or different.

5 Preferably, R^{41} is selected from the group consisting of OH; CH_3 ; and T^3 ;

Preferably, T^3 is T^4 .

10 Preferably, T^4 is phenyl, wherein T^4 is optionally substituted with 1-3 R^{51} , which are the same or different.

Preferably, R^{51} is independently selected from the group consisting of F; Cl; CH_3 ; C_2H_5 ; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3 ; O- CH_3 ; O- C_2H_5 ; S- CH_3 ; and SO_2NH_2 .

15 Preferably, T^3 is T^5 .

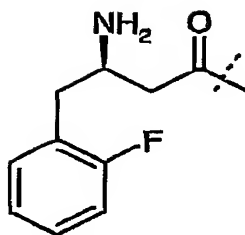
Preferably, T^5 is heterocycle, wherein T^5 is optionally substituted with 1-2 R^{54} , which are the same or different.

20 Preferably, R^{54} is selected from the group consisting of OH; and CH_3 .

Compounds of the formula (I) or (Ia) in which some or all of the above-mentioned groups have the preferred or more preferred meanings are also an object of the present invention.

25 Preferred embodiments of the compounds according to present invention are shown in formula 4 to 98:

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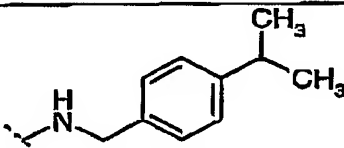
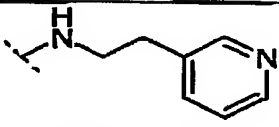
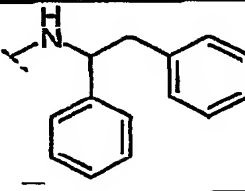
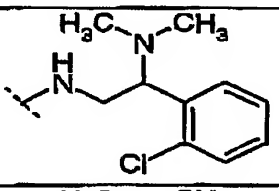
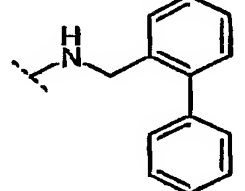
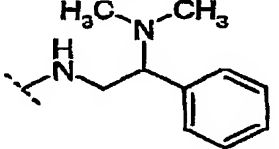
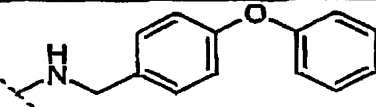
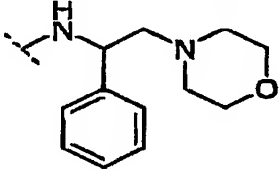
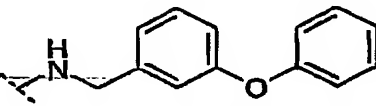
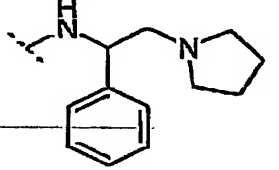
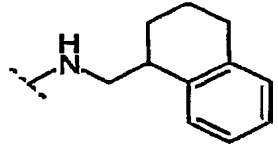
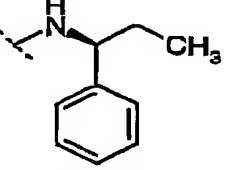
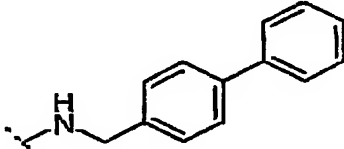
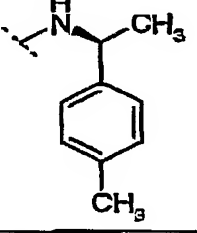
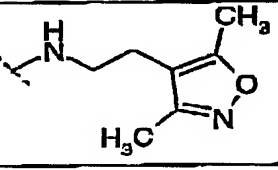
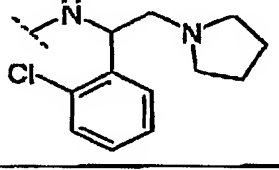
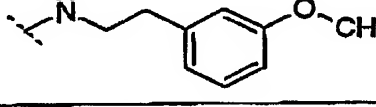
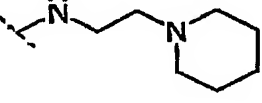
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5	 <chem>*CC(C)NCCc1ccccc1C</chem>
6	 <chem>*CC(C)NCCc1ccccc1SC</chem>
7	 <chem>*CCN(C)CCNC</chem>
8	 <chem>*CCNCCc1ccccn1</chem>
9	 <chem>*CCNCc1ccccc1</chem>
10	 <chem>*CCN[C@H](C)c1ccccc1</chem>
11	 <chem>*CCN[C@H](C)[C@@H]1Cc2ccccc2[C@H]1O</chem>
12	 <chem>*CCNCc1cc(Cl)cc(Cl)cc1</chem>
13	 <chem>*CCN[C@H](Cc1ccc2ccccc2c1)C</chem>
14	 <chem>*CCNCc1cc(F)c(F)cc1</chem>
15	 <chem>*CCN[C@H](C)(Cc1ccccc1)c2ccccc2</chem>
16	 <chem>*CCNCc1ccccn1</chem>
17	 <chem>*CCN[C@H](Cc1ccccc1)C(C)c2ccccc2</chem>
18	 <chem>*CCNCCc1ccccc1</chem>
19	 <chem>*CCNCc1cc(Cl)cc(Cl)cc1</chem>
20	 <chem>*CCNCc1ccccn1</chem>

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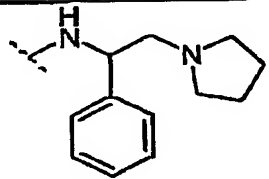
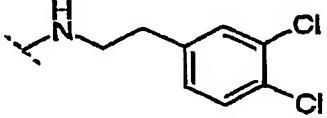
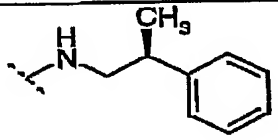
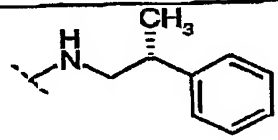
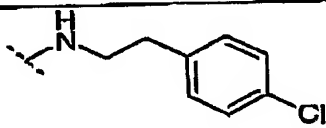
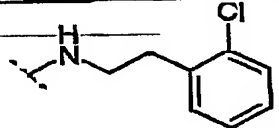
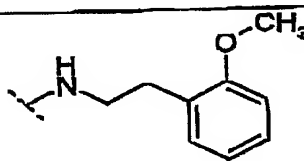
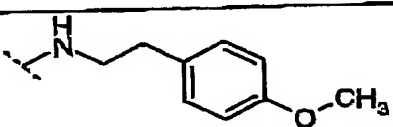
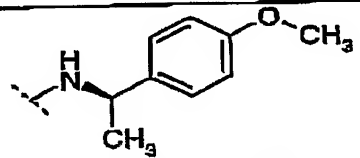
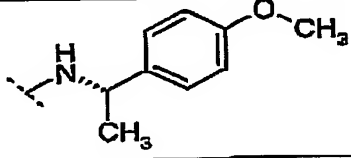
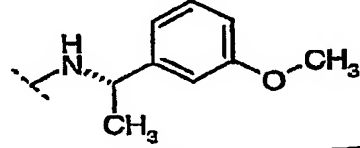
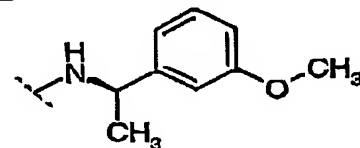
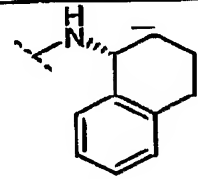
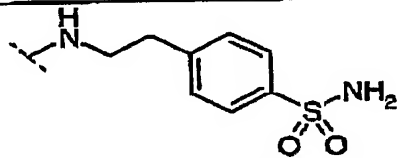
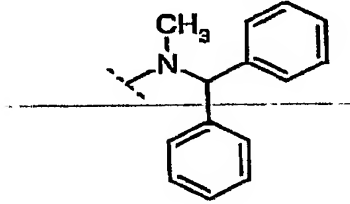
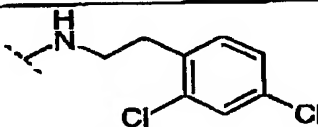
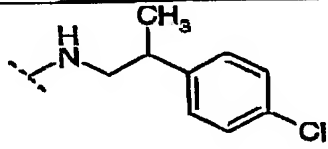
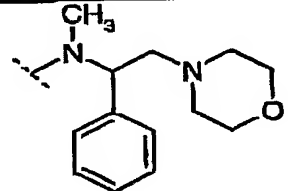
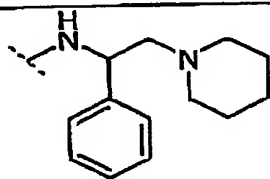
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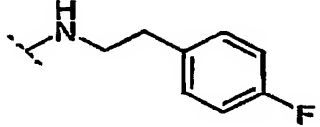
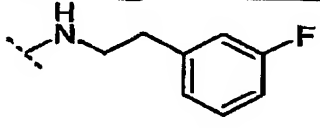
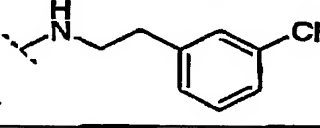
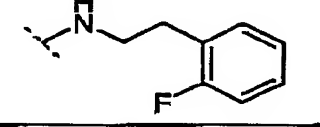
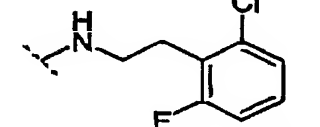
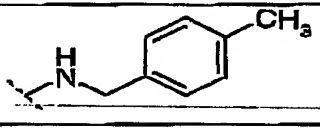
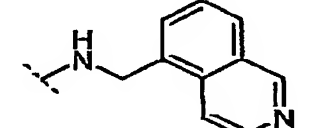
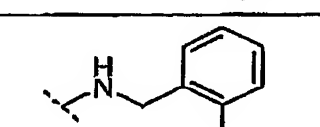
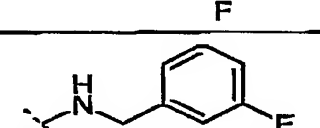
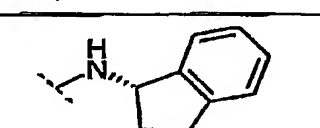
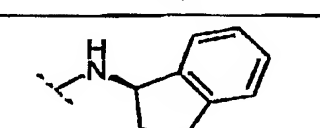
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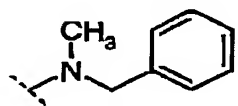
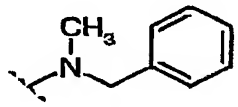
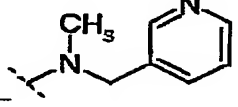
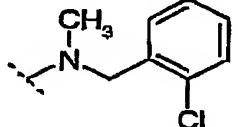
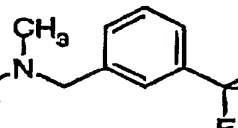
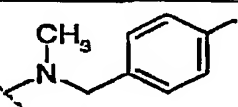
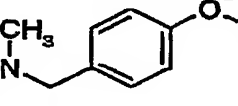
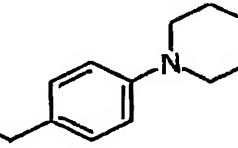
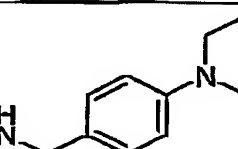
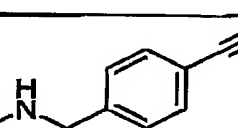
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Furthermore, the present invention provides prodrug compounds of the compounds of the invention as described above.

"Prodrug compound" means a derivative that is converted into a compound according to the present invention by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, e.g. by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically. Examples of the prodrug are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated to form, e.g., eicosanoylamino, alanylaminino, pivaloyloxymethylaminino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated. These compounds can be produced from compounds of the present invention according to well-known methods.

Metabolites of compounds of formula (I) or (Ia) are also within the scope of the present invention.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of general formula (I) or (Ia) or their prodrugs may occur, the individual forms, like e.g. the keto and enol form, are claimed separately and together as mixtures in any ratio. Same applies for stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. Same applies for enantiomers by using e.g. chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e. coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of formula (I) or (Ia) may be obtained from stereoselective synthesis using optically pure starting materials.

In case the compounds according to formula (I) or (Ia) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) or (Ia) which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) or (Ia) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention

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in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, 5 pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) or (Ia) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, 10 inner salts or betaines (zwitterions). The respective salts according to the formula (I) or (Ia) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) or (Ia) which, owing to low 15 physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The present invention provides compounds of general formula (I) or (Ia) or their prodrugs as 20 DPP-IV inhibitors. DPP-IV is a cell surface protein that has been implicated in a wide range of biological functions. It has a broad tissue distribution (intestine, kidney, liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells, serum), and distinct tissue and cell-type expression levels. DPP-IV is identical to the T cell activation marker CD26, and it can cleave a number of immunoregulatory, endocrine, 25 and neurological peptides *in vitro*. This has suggested a potential role for this peptidase in a variety of disease processes.

DPP-IV related diseases are described in more detail in WO-A-03/181 under the paragraph "Utilities" which is herewith incorporated by reference.

30

Accordingly, the present invention provides compounds of formula (I) or (Ia) or their prodrugs or pharmaceutically acceptable salt thereof for use as a medicament.

35

Furthermore, the present invention provides the use of compounds of formula (I) or (Ia) or their prodrugs or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of non-insulin dependent (Type II) diabetes mellitus; hyperglycemia; obesity; insulin resistance; lipid disorders; dyslipidemia; hyperlipidemia; hypertriglyceridemia; hypercholesterolemia; low HDL; high LDL;

atherosclerosis; growth hormone deficiency; diseases related to the immune response; HIV infection; neutropenia; neuronal disorders; tumor metastasis; benign prostatic hypertrophy; gingivitis; hypertension; osteoporosis; diseases related to sperm motility; low glucose tolerance; insulin resistance; its sequelae; vascular restenosis; irritable bowel syndrome; inflammatory bowel disease; including Crohn's disease and ulcerative colitis; other inflammatory conditions; pancreatitis; abdominal obesity; neurodegenerative disease; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type 1 diabetes; or growth hormone deficiency. Preferred is non-insulin dependent (Type II) diabetes mellitus and obesity.

10

The present invention provides pharmaceutical compositions comprising a compound of formula (I) or (Ia), or a prodrug compound thereof, or a pharmaceutically acceptable salt thereof as active ingredient together with a pharmaceutically acceptable carrier.

15 "Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the present invention may additionally comprise one or more other compounds as active ingredients like one or more additional compounds of formula (I) or (Ia), or a prodrug compound or other DPP-IV inhibitors.

25 Other active ingredients are disclosed in WO-A-03/181 under the paragraph "Combination Therapy" which is herewith incorporated by reference.

Accordingly, other active ingredients may be insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-1B (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas and other insulin secretagogues; α -glucosidase inhibitors; glucagon receptor antagonists; GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; GIP, GIP mimetics, and GIP receptor agonists; PACAP, PACAP mimetics, and PACAP receptor 3 agonists; cholesterol lowering agents; HMG-CoA reductase inhibitors; sequestrants; nicotinic alcohol; nicotinic acid or a salt thereof; PPAR α agonists; PPAR α / γ dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPAR γ agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; or anti-inflammatory agents or pharmaceutically acceptable salts of these active compounds.

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The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids.

- 5 The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form
10 and prepared by any of the methods well-known in the art of pharmacy.

- In practical use, the compounds of formula (I) or (Ia) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms
15 depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such
20 as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

- 25 Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be
30 varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

- 35 The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a

capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

5 Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

10 Compounds of formula (I) or (Ia) may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of
15 microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent
20 that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

25 Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of formula (I) or (Ia) are
30 administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person
35 skilled in the art.

When treating or preventing diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of Formula I are indicated, generally satisfactory

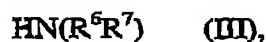
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results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

- 10 Preferred embodiments of compounds having formula (I) of the present invention can be prepared from beta amino acid intermediates such as those of formula (II)



- 15 and substituted amine intermediates such as those of formula (III)



using standard peptide coupling conditions.

20

Some abbreviations that may appear in this application are as follows.

ABBREVIATIONS

Designation

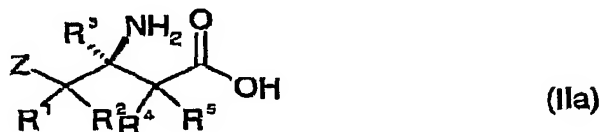
Boc (or BOC)	<i>tert</i> -Butoxycarbonyl
DCM	Dichloromethane
DIEA	Diisopropylethylamine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Et ₃ N	Triethylamine
h	hour
HATU	O-(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
min	minutes

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MTP	Microtiter plate
PG	Protecting group
rt	Retention time
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Available starting materials may be amines having the formula (III), which may be purchased from commercially available sources such as ABCR, Array, Astatech, Sigma-Aldrich, Fluka, or be synthesized by one skilled in the art. Common nucleophilic substitution reactions between compounds containing a suitable leaving group (e.g. halogenide, mesylate, tosylate) and nucleophiles (e.g. amines) may be employed. The conversion of diverse functional groups may allow the synthesis of various amines, e.g. conversion of esters into acids, alcohols or amides intermediates; reduction of amides, nitriles or azides to amines; also novel carbon-nitrogen palladium-catalyzed coupling reactions with suitable functionalized starting materials. For the introduction of changes in the carbon chain attached to the nitrogen atom or for the synthesis of diverse (hetero)aryl derivatives, it may be possible to make use of diverse carbon-carbon coupling reactions, e.g. transition-metal-catalyzed reactions, conventional techniques for ring closure, formylation of (hetero)aryls.

Enantiomerically pure beta amino acids having the formula (IIa)



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may be commercially available, known in the literature or may be conveniently synthesized using one of the methods already published e.g., reviewed in *Aldrichimica Acta*; 27; 3;1994, or *Enantioselective Synthesis of α -Amino Acids*, Ed. Wiley-VCH, New York; 1997.

25

30

Unless otherwise noted, all nonaqueous reactions were carried out under argon atmosphere with commercial dry solvents. Compounds were purified using flash column chromatography using Merck silica gel 60 (230-400 mesh) or reverse phase preparative HPLC using a Reprosil-Pur ODS3, 5 μ m, 20 x 125 mm column with Shimadzu LC8A-Pump and SPD-10Avp UV/Vis diode array detector. The $^1\text{H-NMR}$ spectra were recorded on a Varian VXR-S (300 MHz for $^1\text{H-NMR}$) using d_6 -dimethylsulfoxide as solvent; chemical shifts are reported in ppm relative to tetramethylsilane. Analytical LC/MS was performed

using Reprosil-Pur ODS3, 5 μ M, 1 x 60 mm columns with a linear gradient from 5% to 95% acetonitrile in water (0.1% TFA) at a flow rate of 250 μ l/min; retention times are given in minutes. Methods are:

(I) runs on a LC10Advp-Pump (Shimadzu) with SPD-M10Avp UV/Vis diode array detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214, 254 and 275 nm, 5 min. linear gradient; (II) idem but 3 min. linear gradient; (III) runs on a LC10Advp-Pump (Shimadzu) with SPD-10Avp dual wavelength UV-detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214 and 254 nm, 5 min. linear gradient; (IV) idem but 10 min. linear gradient.

General procedure for making compounds of the invention

In general, compounds having the structure (I)



wherein the variables have the above described meanings, may be prepared in the case of $X = C(O)$ by standard peptide coupling conditions. For example, it may be possible to use 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride in combination with 1-hydroxybenzotriazole (HOBt) and a base (triethylamine or diisopropylethylamine) or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) in the presence of a base, in solvents such as methylene chloride, *N,N*-dimethylformamide or dimethylsulfoxide. In the case of $X = CR^{13}R^{14}$ by reductive amination conditions, for example, it may be possible to use sodium triacetoxyborohydride in acidic media (such as in solvents like methanol or dichloromethane containing acetic acid) in combination with a suitable amine and suitable aldehyde. In the case of $X = CR^{13}R^{14}$ by reduction of an amide carbonyl $C(O)$ group to the corresponding carbon, the amide, prepared as described above, may be reduced with lithium aluminiumhydride in solvents such as tetrahydrofuran. In the case of $X = CR^{13}R^{14}$ by displacement of a suitable leaving group by a suitable amine, the leaving group may be a tosylate, halide, triflate or mesylate reacting with the amine in solvents such as dichloromethane, acetonitrile or *N,N*-dimethylformamide, in the presence of a base such as triethylamine or 2,6-lutidine, for example. In the case of $X = S(O)_2$ this may be prepared by coupling of a suitably prepared sulfonyl chloride with a suitable amine following standard sulfonylation conditions, in solvents such as dichloromethane in the presence of a base such as triethylamine or 2,6-lutidine. In the case of $X = S(O)$ by coupling of a suitable amine with a suitable sulfinyl halide in solvents such as diethylether.

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Scheme A outlines a procedure for using the amines of formula (III) and acids of formula (II) to synthesize preferred compounds that are embodiments of the invention.

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Scheme A

$Z-C(R^1R^2)-C(R^3NHPG)-C(R^4R^5)-COOH + N(R^6R^7) \xrightarrow{\text{coupling reaction (step 1)}}$

$Z-C(R^1R^2)-C(R^3NHPG)-C(R^4R^5)-C(O)-N(R^6R^7) \xrightarrow{\text{deprotection (step 2)}}$

10

$Z-C(R^1R^2)-C(R^3NH_2)-C(R^4R^5)-C(O)-N(R^6R^7)$

15

The protective group may be removed with, for example, diethylamine in dichloromethane in the case of Fmoc or using acidic conditions (such as trifluoroacetic acid in dichloromethane or hydrochloric acid in dioxane) in the case of Boc, as described in *Protective Groups in Organic Synthesis* 3rd ed., Ed. Wiley-VCH, New York; 1999.

For the purification of intermediates or end products, flash chromatography on silica gel may be suitable for the isolation of free amines whereas the use of preparative HPLC leads to the isolation of the corresponding trifluoroacetic acid salts.

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Compounds may be prepared by other means, however, and the suggested starting materials and procedures described below are exemplary only and should not be considered as limiting the scope of the invention.

25

EXAMPLES

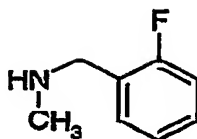
The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

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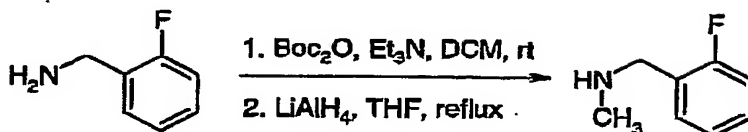
PREPARATIONS**Example 1**

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Procedure for making an intermediate according to Scheme C.



(2-Fluoro-benzyl)-methyl amine.

To a solution of 300 mg (2.40 mmol) of 2-fluorobenzylamine, 29.3 mg (0.24 mmol) of 4-dimethylaminopyridine and 342 μ l (2.64 mmol) of triethylamine in 3 mL of dichloromethane is added 628 mg (2.88 mmol) of di(*tert*-butoxycarbonyl) in 3 mL of dichloromethane at 0 °C. The reaction is allowed to react during 72 h and solvents are removed under reduced pressure. The crude product is dissolved in 5 mL of 1N hydrochloric acid solution and extracted three times with ethyl acetate. The organic phase is separated and washed with saturated sodium bicarbonate solution and brine and dried with sodium sulfate. Removal of the solvent affords (2-fluoro-benzyl)-carbamic acid *tert*-butyl ester, which is taken directly onto the next step.

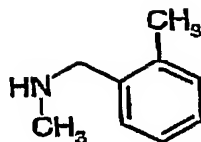
To a solution of 250 mg (1.11 mmol) of the carbamic ester in 1 mL of tetrahydrofuran is added 1.66 mL of a 1M lithium aluminiumhydride solution in tetrahydrofuran. The reaction mixture is stirred at room temperature until gas evolution has ceased and is further heated at reflux temperature for 3 h. After cooling to room temperature, 1N hydrochloric acid solution is added, followed by saturated sodium bicarbonate solution and extraction with dichloromethane. The aqueous phase is separated, a saturated sodium bicarbonate solution is added until pH reaches 7-8 and dichloromethane is added. The organic layer is extracted with brine and water, dried with sodium sulfate and concentrated under vacuum to obtain the title compound.

LC/MS (III) rt 1.52, m/z 140 [M+H]⁺.

According to the procedure outline above, following compounds were prepared.

Example 2

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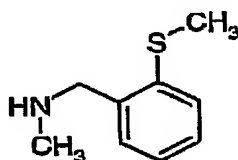


Methyl-(2-methyl-benzyl)-amine.

Obtained from 2-methyl-benzylamine.

5 LC/MS (III) rt 1.67, m/z 177 [M+Na+H]⁺.

Example 3



10

Methyl-(2-methylsulfanyl-benzyl)-amine.

Obtained from 2-methylsulfanyl-benzylamine.

LC/MS (I) rt 1.76, m/z 168 [M+H]⁺.

15

Following examples deal with compounds of the invention synthesized according to Scheme

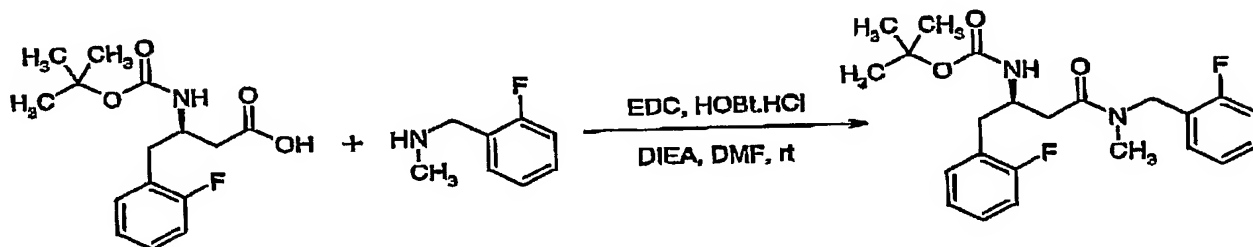
A.

A description of the general procedures used for Steps 1 and 2 follows.

20

Example 4

Step 1



25

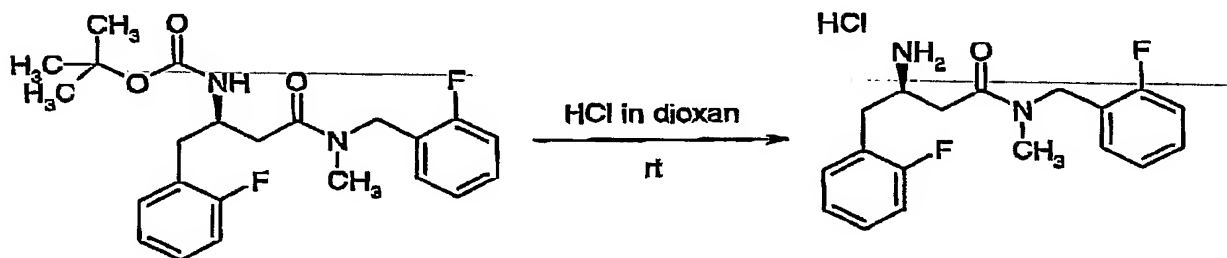
- 30 -

[1-(R)-{[(2-Fluoro-benzyl)-methyl-carbamoyl]-methyl}-2-(2-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester.

A mixture of 20.0 mg (0.07 mmol) of (3*R*)-*tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid, 12.8 mg (0.09 mmol) of 1-hydroxybenzotriazole, 18.1 mg (0.09 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 38 μ L (0.29 mmol) of diisopropylethylamine in 1.5 mL of *N,N*-dimethylformamide is stirred for 5 min. After addition of 11.8 mg (0.08 mmol) of (2-fluoro-benzyl)-methyl amine (Example 1) in 0.5 mL of *N,N*-dimethylformamide, the mixture is stirred for further 16 h. The solution is diluted with 5 mL of 1N hydrochloric acid solution and extracted twice with 10 mL of dichloromethane. The collected organic phases are washed with brine and water, dried over sodium sulfate and evaporated under reduced pressure. The residue is purified using flash chromatography (silica gel, eluent: 0% to 20% ethyl acetate in cyclohexane) to afford the title compound.

LC/MS (I) rt 3,24, m/z 419 (M+H).

Step 2



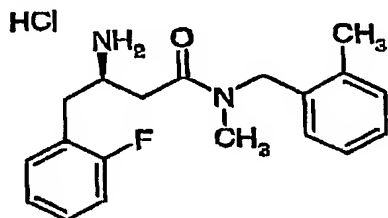
(3*R*)-Amino-*N*-(2-fluoro-benzyl)-4-(2-fluoro-phenyl)-*N*-methyl-butamide hydrochloride.

A solution of 20.0 mg (0.04 mmol) of [1-(R)-{[(2-fluoro-benzyl)-methyl-carbamoyl]-methyl}-2-(2-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester in 1.0 mL of 4N hydrochloric acid solution in dioxan is stirred for 2 h and then evaporated under reduced pressure. The crude mixture is diluted in methanol and again evaporated under vacuum to afford 17.0 mg (quant.) of the title compound.

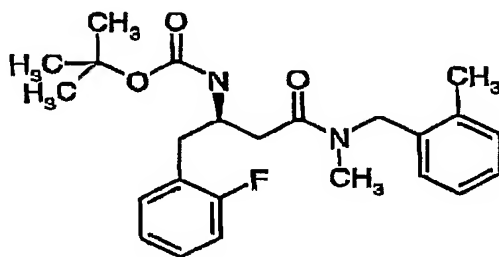
¹H-NMR δ (ppm) = 2.65-2.88 (m, 5H), 2.95-3.15 (m, 2H), 3.67 (m, 2H), 4.27-4.53 (2m, 1H), 7.10-7.33 (m, 8H), 8.28 (bs, 2H).

LC/MS (I) rt 2,13, m/z 319 [M+H]⁺.

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Example 5

- 5 Prepared following the procedure above outlined for Example 4 according to Scheme A.

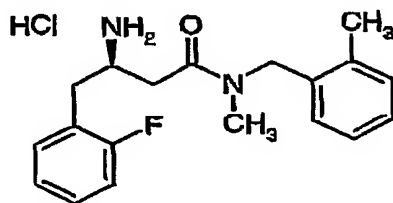
Step 1

10

(2-(2-Fluoro-phenyl)-1-([methyl-(2-methyl-benzyl)-carbamoyl]-methyl)-ethyl)-carbamic acid tert-butyl ester.

Obtained from (3*R*)-*tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid and methyl-(2-methyl-benzyl)-amine (Example 2).

- 15 LC/MS (I) rt 3,37, m/z 415 [M+H]⁺.

Step 2

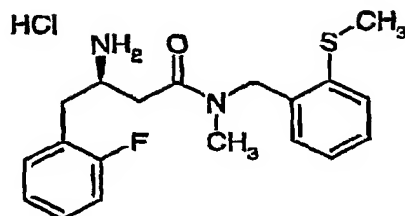
- 20 3-Amino-4-(2-fluoro-phenyl)-N-methyl-N-(2-methyl-benzyl)-butyramide hydrochloride.

Obtained from (2-(2-fluoro-phenyl)-1-([methyl-(2-methyl-benzyl)-carbamoyl]-methyl)-ethyl)-carbamic acid tert-butyl ester according to Step 2 in the procedure described for Example 4.

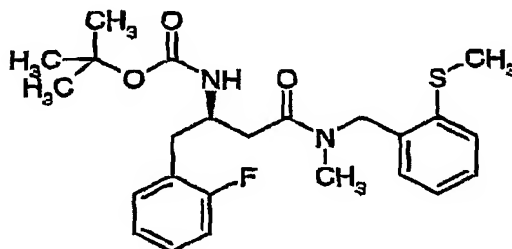
LC/MS (I) rt 2,30, m/z 315 [M+H]⁺.

25

- 32 -

Example 6

5 Prepared following the procedure outlined for Example 4 according to Scheme A.

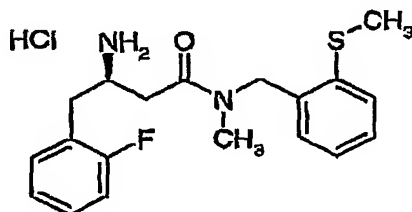
Step 1

10

(2-(2-Fluoro-phenyl)-1-[[methyl-(2-methylsulfanyl-benzyl)-carbamoyl]-methyl]-ethyl)-
carbamic acid tert-butyl ester.

Obtained from (3*R*)-*tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid and methyl-(2-methylsulfanyl-benzyl)-amine (Example 3).

15 LC/MS (I) rt 3,31 , m/z 415 [M+H]⁺.

Step 2

20

3-Amino-4-(2-fluoro-phenyl)-N-methyl-N-(2-methylsulfanyl-benzyl)-butyramide
hydrochloride.

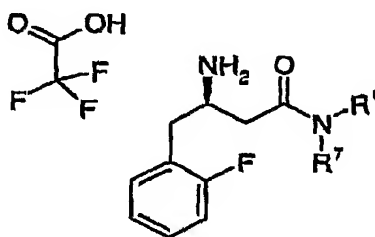
- 33 -

Obtained from (2-(2-fluoro-phenyl)-1-([methyl-(2-methylsulfanyl-benzyl)-carbamoyl]-methyl)-ethyl)-carbamic acid tert-butyl ester according to Step 2 in the procedure described for Example 4.

LC/MS (I) rt 2,30, m/z 315 [M+H]⁺.

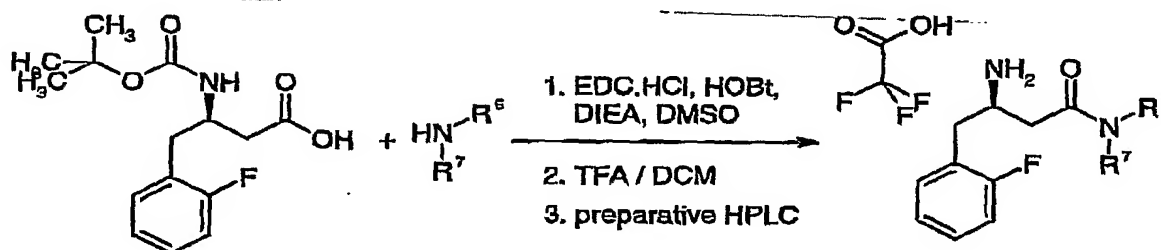
5

Compounds listed in Table 1 with the formula



10

were prepared according to the following experimental procedure:



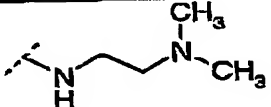
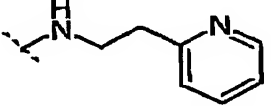
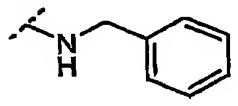
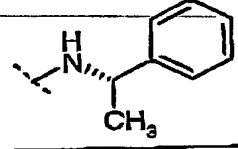
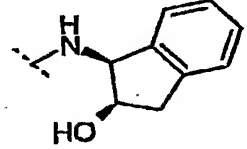
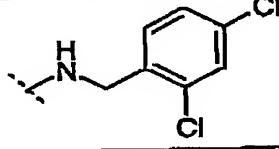
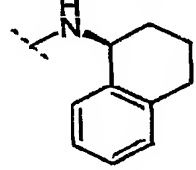
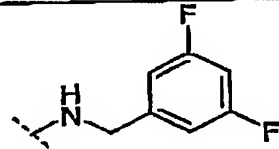
15

To 100 μ L of a 0.5M dimethylsulfoxide solution of (3R)-tert-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid in a well of a 96-MTP are added sequentially 140 μ L of a 0.5M dimethylsulfoxide solution of 1-hydroxybenzotriazole, 140 μ L of a 0.5M dimethylsulfoxide solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 20 μ L (0.15 mmol) of diisopropylethylamine. After 15 min. at room temperature 0.06 mmol of the corresponding amine dissolved in 100 μ L of dimethylsulfoxide is added and the reaction mixture is stirred overnight at room temperature. Solvents are removed under vacuum, 500 μ L of a solution of trifluoroacetic acid in dichloromethane (33% v/v) is added and the reaction mixture is stirred for 2 h at room temperature. After removal of the solvents under reduced pressure, 500 μ L of methanol are added and the crude material is purified using

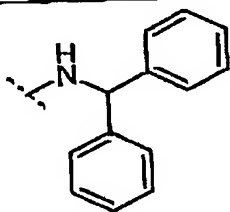
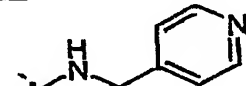
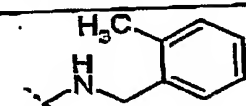
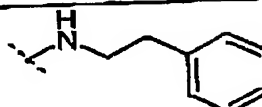
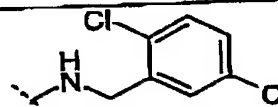

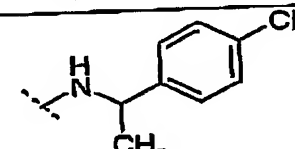
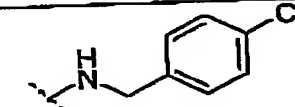
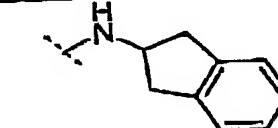
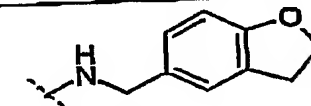
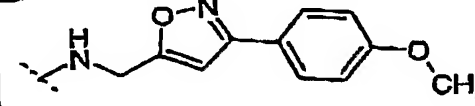
25

preparative HPLC with a 10 min. linear gradient from 5% to 95% acetonitrile in water (0.1% TFA) to afford the title compounds.

TABLE 1

Ex.	R^6R^7N-	LC/MS data m/z	LC/MS data rt (min) Method IV
7		268 $[M+H]^+$	1,76
8		302 $[M+H]^+$	2,08
9		287 $[M+H]^+$	2,08 (Methode III)
10		301 $[M+H]^+$	4,94
11		329 $[M+H]^+$	4,24
12		355 $[M+H]^+$	5,72
13		327 $[M+H]^+$	5,56
14		323 $[M+H]^+$	5,08

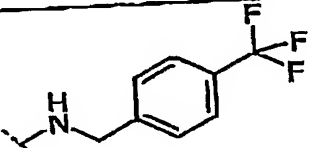
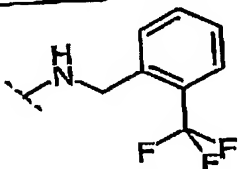
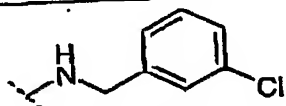
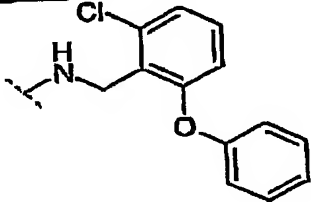
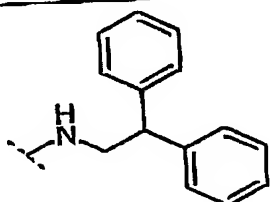
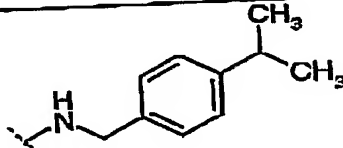
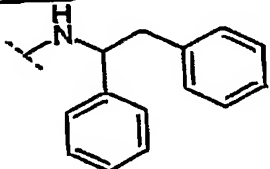
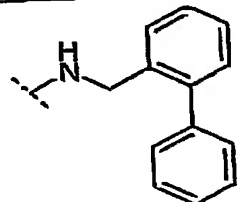
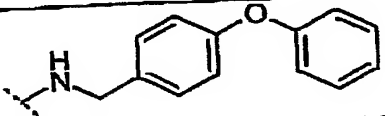
- 35 -

15		363 [M+H] ⁺	6,18
16		288 [M+H] ⁺	1,87
17		301 [M+H] ⁺	5,04
18		301 [M+H] ⁺	4,97
19		355 [M+H] ⁺	5,67
20		288 [M+H] ⁺	1,99
21		376 [M+CH ₃ CN+H] ⁺	5,63
22		321 [M+H] ⁺	3,34
23		313 [M+H] ⁺	5,22
24		329 [M+H] ⁺	4,73
25		384 [M+H] ⁺	5,37

- 36 -

26		288 [M+H] ⁺	1,59
27		341 [M+H] ⁺	5,48
28		373 [M+H] ⁺	5,84
29		345 [M+H] ⁺	4,75
30		292 [M+H] ⁺	3,60
31		353 [M+H] ⁺	4,83
32		363 [M+H] ⁺	6,32
33		341 [M+H] ⁺	5,36
34		303 [M+H] ⁺	3,09
35		343 [M+H] ⁺	4,99

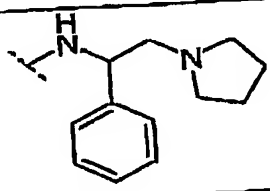
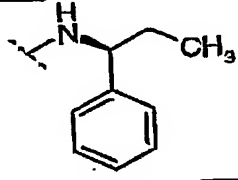
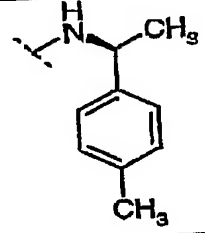
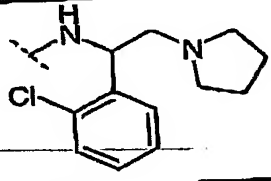
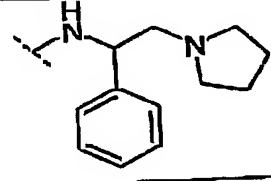
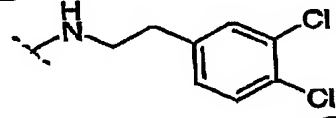
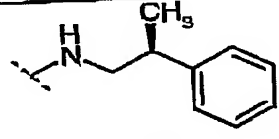
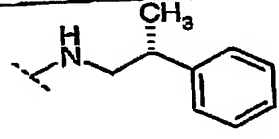
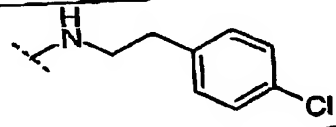
- 37 -

36		355 [M+H] ⁺	5,75
37		355 [M+H] ⁺	5,52
38		321 [M+H] ⁺	5,34
39		413 [M+H] ⁺	6,59
40		377 [M+H] ⁺	6,34
41		329 [M+H] ⁺	6,02
42		377 [M+H] ⁺	2,55 (Method I)
43		363 [M+H] ⁺	6,25
44		379 [M+H] ⁺	6,42

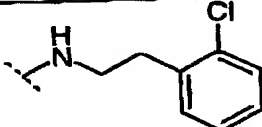
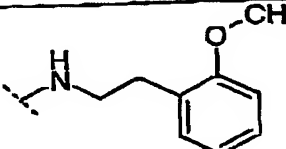
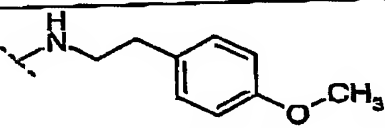
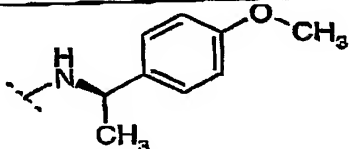
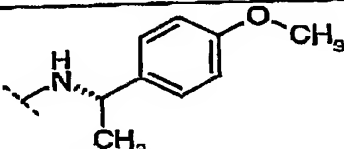
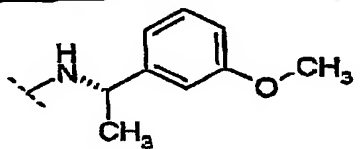
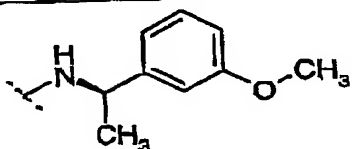
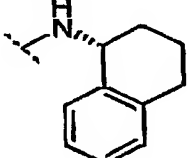
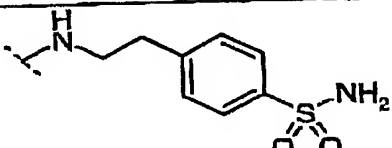
- 38 -

45		379 [M+H] ⁺	6,39
46		341 [M+H] ⁺	5,98
47		363 [M+H] ⁺	6,42
48		320 [M+H] ⁺	4,04
49		331 [M+H] ⁺	5,01
50		308 [M+H] ⁺	2,42
51		302 [M+H] ⁺	2,18
52		378 [M+H] ⁺	1,54 (Method II)
53		344 [M+H] ⁺	3,28
54		386 [M+H] ⁺	1,52 (Method II)

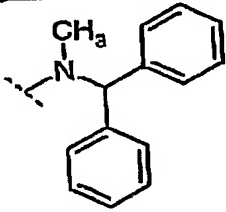
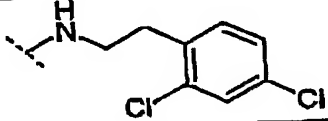
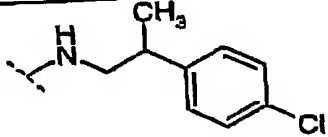
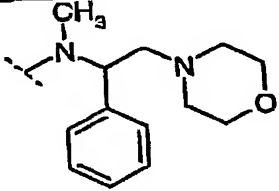
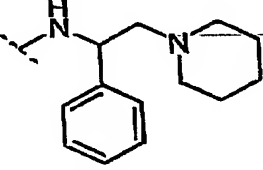
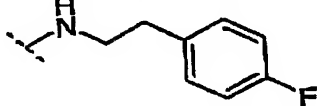
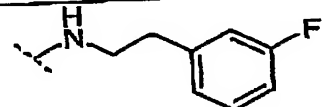
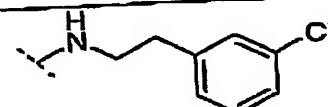
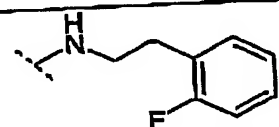
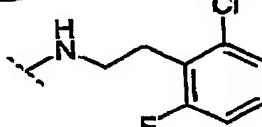
- 39 -

55		370 [M+H] ⁺	1,52 (Method II)
56		315 [M+H] ⁺	5,38
57		315 [M+H] ⁺	5,57
58		404 [M+H] ⁺	1,55 (Method II)
59		370 [M+H] ⁺	1,54 (Method II)
60		369 [M+H] ⁺	6,15
61		315 [M+H] ⁺	5,48
62		315 [M+H] ⁺	5,46
63		335 [M+H] ⁺	5,77

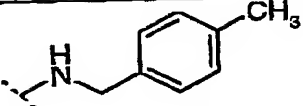
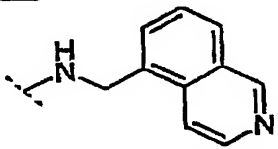
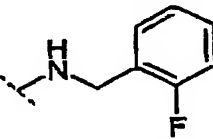
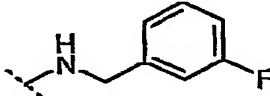
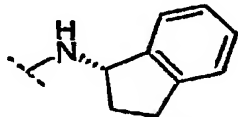
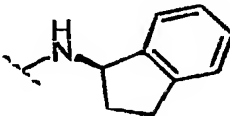
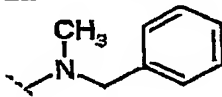
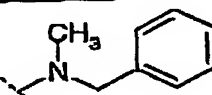
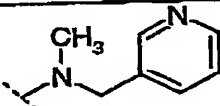
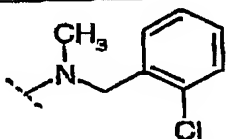
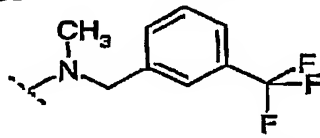
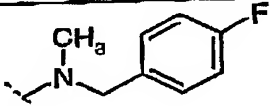
- 40 -

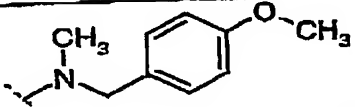
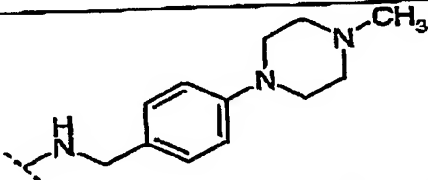
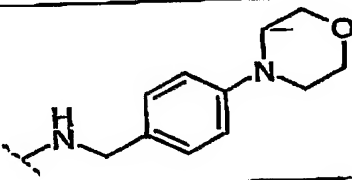
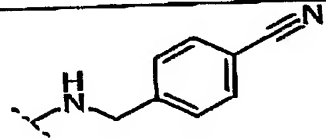
64		335 [M+H] ⁺	5,65
65		331 [M+H] ⁺	5,44
66		331 [M+H] ⁺	4,95
67		331 [M+H] ⁺	5,82
68		331 [M+H] ⁺	4,99
69		331 [M+H] ⁺	5,30
70		331 [M+H] ⁺	5,30
71		327 [M+H] ⁺	5,82
72		380 [M+H] ⁺	3,97

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73		377 [M+H] ⁺	6,88
74		371 [M+H] ⁺	6,26
75		349 [M+H] ⁺	5,91
76		400 [M+H] ⁺	2,02 (Method I)
77		384 [M+H] ⁺	1,52 (Method II)
78		319 [M+H] ⁺	5,49
79		319 [M+H] ⁺	5,50
80		335 [M+H] ⁺	5,92
81		319 [M+H] ⁺	5,46
82		353 [M+H] ⁺	5,45

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83		301 [M+H] ⁺	5,44
84		338 [M+H] ⁺	3,14
85		305 [M+H] ⁺	2,01 (Method I)
86		305 [M+H] ⁺	2,11 (Method I)
87		313 [M+H] ⁺	2,20 (Method I)
88		313 [M+H] ⁺	2,18 (Method I)
89		301 [M+H] ⁺	2,16 (Method I)
90		301 [M+H] ⁺	2,16 (Method I)
91		302 [M+H] ⁺	1,42
92		335 [M+H] ⁺	3,42
93		369 [M+H] ⁺	3,55
94		319 [M+H] ⁺	3,13

95		331 [M+H] ⁺	3,19
96		385 [M+H] ⁺	2,47
97		372 [M+H] ⁺	2,61
98		312 [M+H] ⁺	2,93

ASSAYS

5

Inhibition of DPP-IV peptidase activity was monitored with a continuous fluorimetric assay. This assay is based on the cleavage of the substrate Gly-Pro-AMC (Bachem) by DPP-IV, releasing free AMC. The assay is carried out in 96-well microtiterplates. In a total volume of 100 μ l, compounds are preincubated with 50 pM DPP-IV employing a buffer containing 10mM Hepes, 150mM NaCl, 0.005% Tween 20 (pH 7.4). The reaction is started by the addition of 16 μ M substrate and the fluorescence of liberated AMC is detected for 10 minutes at 25 °C with a fluorescence reader (BMG-Fluostar; BMG-Technologies) using an excitation wavelength of 370 nm and an emission wavelength of 450 nm. The final concentration of DMSO is 1 %. The inhibitory potential of the compounds were determined. DPP-IV activity assays were carried out with human and porcine DPP-IV (see below); both enzymes showed comparable activities.

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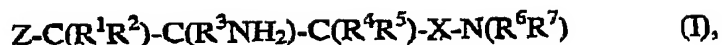
Soluble human DPP-IV lacking the transmembrane anchor (Gly31-Pro766) was expressed in a recombinant YEAST-strain as Pre-Pro-alpha-mating fusion. The secreted product (rhDPP-IV-Gly31-Pro766) was purified from fermentation broth (>90% purity).

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The examples 4-98 show a % inhibition of about 2 μ M or less.

Claims

1. A compound of the formula (I)



or a pharmaceutically acceptable salt thereof, wherein

Z is selected from the group consisting of phenyl; naphthyl; indenyl; C₃₋₇ cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R⁸, wherein R⁸ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; R⁹; and R¹⁰;

R⁹ is selected from the group consisting of C₁₋₆ alkyl; O-C₁₋₆ alkyl; and S-C₁₋₆ alkyl, wherein R⁹ is optionally interrupted by oxygen and wherein R⁹ is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R¹⁰ is selected from the group consisting of phenyl; heterocycle; and C₃₋₇ cycloalkyl, wherein R¹⁰ is optionally substituted with one or more R¹¹, wherein R¹¹ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; C₁₋₆ alkyl; O-C₁₋₆ alkyl; and S-C₁₋₆ alkyl;

R¹, R⁴ are independently selected from the group consisting of H; F; OH; and R^{4a};

R², R⁵ are independently selected from the group consisting of H; F; and R^{4b};

R^{4a} is independently selected from the group consisting of C₁₋₆ alkyl; and O-C₁₋₆ alkyl, wherein R^{4a} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{4b} is C₁₋₆ alkyl, wherein R^{4b} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R³ is selected from the group consisting of H; and C₁₋₆ alkyl;

Optionally one or more pairs of R¹, R², R³, R⁴, R⁵ independently selected from the group consisting of R¹/R²; R²/R³; R³/R⁴; and R⁴/R⁵ form a C₃₋₇ cycloalkyl ring, which is optionally

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substituted with one or more of R^{12} , wherein R^{12} is independently selected from the group consisting of F; Cl; and OH;

X is selected from the group consisting of S(O); S(O)₂; C(O); and C(R¹³R¹⁴);

R¹³, R¹⁴ are independently selected from the group consisting of H; F; C₁₋₆ alkyl; R¹⁵; and R¹⁶;

Optionally one or both pairs of R⁵, R¹³, R¹⁴ selected from the group consisting of R⁵/R¹³; and R¹³/R¹⁴ form a C₃₋₇ cycloalkyl ring, which is optionally substituted with one or more R¹⁷, wherein R¹⁷ is independently selected from the group consisting of F; Cl; and OH;

R¹⁵ is selected from the group consisting of phenyl; naphthyl; and indenyl, wherein R¹⁵ is optionally substituted with one or more R¹⁸, wherein R¹⁸ is independently selected from the group consisting of R¹⁹; R²⁰; halogen; CN; COOH; OH; C(O)NH₂; S(O)₂NH₂; S(O)NH₂; C₁₋₆ alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R²¹)-C₁₋₆ alkyl; S(O)₂N(R²¹)-C₁₋₆ alkyl; S(O)N(R²¹)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; N(R²¹)S(O)₂-C₁₋₆ alkyl; and N(R²¹)S(O)-C₁₋₆ alkyl, wherein each C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R¹⁶ is selected from the group consisting of heterocycle; heterobicycle; C₃₋₇ cycloalkyl; indanyl; tertralinyl; and decalinyl, wherein R¹⁶ is optionally substituted with one or more R²², wherein R²² is independently selected from the group consisting of R¹⁹; R²⁰; halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH₂; COOH; C(O)NH₂; S(O)₂NH₂; S(O)NH₂; C₁₋₆ alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; N(R²³)-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R²³)-C₁₋₆ alkyl; N(R²³)-C(O)-C₁₋₆ alkyl; S(O)₂N(R²³)-C₁₋₆ alkyl; S(O)N(R²³)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; N(R²³)S(O)₂-C₁₋₆ alkyl; and N(R²³)S(O)-C₁₋₆ alkyl, wherein each C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R¹⁹ is selected from the group consisting of phenyl; and naphthyl, wherein R¹⁹ is optionally substituted with one or more R²⁴, wherein R²⁴ is independently selected from the group consisting of halogen; CN; COOH; OH; C(O)NH₂; S(O)₂NH₂; S(O)NH₂; C₁₋₆ alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R²⁵)-C₁₋₆ alkyl; S(O)₂N(R²⁵)-C₁₋₆ alkyl; S(O)N(R²⁵)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; N(R²⁵)S(O)₂-C₁₋₆ alkyl; and N(R²⁵)S(O)-C₁₋₆ alkyl, wherein each

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C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R²⁰ is selected from the group consisting of heterocycle; heterobicycle; and C₃₋₇ cycloalkyl; wherein R²⁰ is optionally substituted with one or more R²⁶, wherein R²⁶ is independently selected from the group consisting of halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH₂; COOH; C(O)NH₂; S(O)₂NH₂; S(O)NH₂; C₁₋₆ alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; N(R²⁷)-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R²⁷)-C₁₋₆ alkyl; N(R²⁷)-C(O)-C₁₋₆ alkyl; S(O)₂N(R²⁷)-C₁₋₆ alkyl; S(O)N(R²⁷)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; N(R²⁷)S(O)₂-C₁₋₆ alkyl; and N(R²⁷)S(O)-C₁₋₆ alkyl wherein each C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R²¹, R²³, R²⁵, R²⁷ are independently selected from the group consisting of H; and C₁₋₆alkyl, which is optionally substituted with one or more of R²⁸, wherein R²⁸ is independently selected from the group consisting of F; Cl and OH;

R⁶, R⁷ are independently selected from the group consisting of H; (C(R²⁹R³⁰))_m-X¹-Z¹; and (C(R³¹R³²))_n-X²-X³-Z², provided that R⁶, R⁷ are selected so that not both of R⁶, R⁷ are independently selected from the group consisting of H; CH₃; CH₂CH₃; CH₂CH₂CH₃; and CH(CH₃)₂;

Optionally R⁶, R⁷ are independently C₁₋₄ alkyl, which is substituted with one or more R^{29a}, wherein R^{29a} is independently selected from the group consisting of R^{29b}; and Z¹, provided that R⁶, R⁷ are selected so that not both of R⁶, R⁷ are independently selected from the group consisting of CH₃; CH₂CH₃; CH₂CH₂CH₃; and CH(CH₃)₂;

R²⁹, R^{29b}, R³⁰, R³¹, R³² are independently selected from the group consisting of H; halogen; CN; OH; NH₂; COOH; C(O)NH₂; S(O)₂NH₂; S(O)NH₂; C₁₋₆ alkyl; O-C₁₋₆ alkyl; N(R^{32a})-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R^{32a})-C₁₋₆ alkyl; N(R^{32a})-C(O)-C₁₋₆ alkyl; S(O)₂N(R^{32a})-C₁₋₆ alkyl; S(O)N(R^{32a})-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; N(R^{32a})S(O)₂-C₁₋₆ alkyl; and N(R^{32a})S(O)-C₁₋₆ alkyl wherein each C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{32a} is selected from the group consisting of H; and C₁₋₆ alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

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Optionally one or more pairs of R^{29} , R^{30} , R^{31} , R^{32} independently selected from the group consisting of R^{29}/R^{30} ; and R^{31}/R^{32} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{32b} , wherein R^{32b} is independently selected from the group consisting of F; Cl; and OH;

m is 0, 1, 2, 3 or 4;

n is 2, 3 or 4;

X^1 is independently selected from the group consisting of a covalent bond; $-C_{1-6}$ alkyl-; $-C_{1-6}$ alkyl-O-; $-C_{1-6}$ alkyl- $N(R^{33})$ -; $-C(O)$ -; $-C(O)-C_{1-6}$ alkyl-; $-C(O)-C_{1-6}$ alkyl-O-; $-C(O)-C_{1-6}$ alkyl- $N(R^{33})$ -; $-C(O)O$ -; $-C(O)O-C_{1-6}$ alkyl-; $-C(O)O-C_{1-6}$ alkyl-O-; $-C(O)O-C_{1-6}$ alkyl- $N(R^{33})$ -; $-C(O)N(R^{33})$ -; $-C(O)N(R^{33})-C_{1-6}$ alkyl-; $-C(O)N(R^{33})-C_{1-6}$ alkyl-O-; $-C(O)N(R^{33})-C_{1-6}$ alkyl- $N(R^{34})$ -; $-S(O)_2$ -; $-S(O)$ -; $-S(O)_2-C_{1-6}$ alkyl-; $-S(O)-C_{1-6}$ alkyl-; $-S(O)_2-C_{1-6}$ alkyl-O-; $-S(O)-C_{1-6}$ alkyl-O-; $-S(O)_2-C_{1-6}$ alkyl- $N(R^{33})$ -; and $-S(O)-C_{1-6}$ alkyl- $N(R^{33})$ -; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

X^2 is selected from the group consisting of $-O$ -; $-S$ -; $-S(O)$ -; $S(O)_2$ -; and $-N(R^{35})$ -;

X^3 is selected from the group consisting of a covalent bond; $-C_{1-6}$ alkyl-; $-C_{1-6}$ alkyl-O-; $-C_{1-6}$ alkyl- $N(R^{36})$ -; $-C(O)$ -; $-C(O)-C_{1-6}$ alkyl-; $-C(O)-C_{1-6}$ alkyl-O-; $-C(O)-C_{1-6}$ alkyl- $N(R^{36})$ -; $-C(O)O$ -; $-C(O)O-C_{1-6}$ alkyl-; $-C(O)O-C_{1-6}$ alkyl-O-; $-C(O)O-C_{1-6}$ alkyl- $N(R^{36})$ -; $-C(O)N(R^{36})$ -; $-C(O)N(R^{36})-C_{1-6}$ alkyl-; $-C(O)N(R^{36})-C_{1-6}$ alkyl-O-; and $-C(O)N(R^{36})-C_{1-6}$ alkyl- $N(R^{37})$ -; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally X^2-X^3 are independently selected from the group consisting of $-N(R^{35})-S(O)_2$ -; $-N(R^{35})-S(O)$ -; $-N(R^{35})-S(O)_2-C_{1-6}$ alkyl-; $-N(R^{35})-S(O)-C_{1-6}$ alkyl-; $-N(R^{35})-S(O)_2-C_{1-6}$ alkyl-O-; $-N(R^{35})-S(O)-C_{1-6}$ alkyl-O-; $-N(R^{35})-S(O)_2-C_{1-6}$ alkyl- $N(R^{36})$ -; and $-N(R^{35})-S(O)-C_{1-6}$ alkyl- $N(R^{36})$ -; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{33} , R^{34} , R^{35} , R^{36} , R^{37} are independently selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Z^1 , Z^2 are independently selected from the group consisting of Z^3 ; and $-C(R^{37a})Z^{3a}Z^{3b}$;

R^{37a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more F;

Z^3 , Z^{3a} , Z^{3b} are independently selected from the group consisting of H; T^1 ; T^2 ; C_{1-6} alkyl; C_{1-6} alkyl- T^1 ; and C_{1-6} alkyl- T^2 ; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{37b} , wherein R^{37b} is independently selected from the group consisting of halogen; CN; OH; NH_2 ; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; $N(R^{37c})$ - C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{37c})$ - C_{1-6} alkyl; $N(R^{37c})$ -C(O)- C_{1-6} alkyl; $S(O)_2N(R^{37c})$ - C_{1-6} alkyl; $S(O)N(R^{37c})$ - C_{1-6} alkyl; $S(O)_2$ - C_{1-6} alkyl; $S(O)$ - C_{1-6} alkyl; $N(R^{37c})S(O)_2$ - C_{1-6} alkyl; and $N(R^{37c})S(O)$ - C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

T^1 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^1 is optionally substituted with one or more R^{38} ; wherein R^{38} is independently selected from the group consisting of halogen; CN; R^{39} ; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; COOT³; OT³; ST³; $C(O)N(R^{40})T^3$; $S(O)_2N(R^{40})T^3$; $S(O)N(R^{40})T^3$ and T^3 ;

T^2 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein T^2 is optionally substituted with one or more R^{41} , wherein R^{41} is independently selected from the group consisting of halogen; CN; R^{42} ; OH; oxo (=O), where the ring is at least partially saturated; NH_2 ; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; COOT³; OT³; $C(O)N(R^{43})T^3$; $S(O)_2N(R^{43})T^3$; $S(O)N(R^{43})T^3$; $N(R^{43})T^3$; and T^3 ;

R^{39} is selected from the group consisting of C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{44})$ - C_{1-6} alkyl; $S(O)_2N(R^{44})$ - C_{1-6} alkyl; $S(O)N(R^{44})$ - C_{1-6} alkyl; $S(O)$ - C_{1-6} alkyl; $S(O)_2$ - C_{1-6} alkyl; $N(R^{44})S(O)_2$ - C_{1-6} alkyl; and $N(R^{44})S(O)$ - C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more R^{45} , wherein R^{45} is independently selected from the group consisting of F; COOR⁴⁶; $C(O)N(R^{46}R^{47})$; $S(O)_2N(R^{46}R^{47})$; OR⁴⁶; $N(R^{46}R^{47})$; T³; O-T³; and $N(R^{46})$ -T³;

R^{42} is selected from the group consisting of C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; $N(R^{48})$ - C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{48})$ - C_{1-6} alkyl; $N(R^{48})$ -C(O)- C_{1-6} alkyl; $S(O)_2N(R^{48})$ - C_{1-6} alkyl; $S(O)N(R^{48})$ - C_{1-6} alkyl; $S(O)$ - C_{1-6} alkyl; $S(O)_2$ - C_{1-6} alkyl; $-N(R^{48})S(O)_2$ - C_{1-6} alkyl; and $-N(R^{48})S(O)$ - C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally

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substituted with one or more R^{45} , wherein R^{45} is independently selected from the group consisting of F; COOR^{49} ; $\text{C(O)N(R}^{49}\text{R}^{50})$; $\text{S(O)}_2\text{N(R}^{49}\text{R}^{50})$; $\text{S(O)N(R}^{49}\text{R}^{50})$; OR^{49} ; $\text{N(R}^{49}\text{R}^{50})$; T^3 ; O-T^3 ; and $\text{N(R}^{49})\text{-T}^3$;

R^{40} , R^{43} , R^{44} , R^{46} , R^{47} , R^{48} , R^{49} , R^{50} are independently selected from the group consisting of H; and C_{1-6} alkyl;

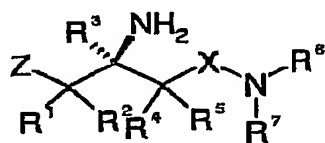
T^3 is selected from the group consisting of T^4 ; and T^5 ;

T^4 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^4 is optionally substituted with one or more R^{51} , wherein R^{51} is independently selected from the group consisting of halogen; CN; COOR^{52} ; OR^{52} ; $\text{C(O)N(R}^{52}\text{R}^{53})$; $\text{S(O)}_2\text{N(R}^{52}\text{R}^{53})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $\text{C(O)N(R}^{52})\text{-C}_{1-6}$ alkyl; $\text{S(O)}_2\text{N(R}^{52})\text{-C}_{1-6}$ alkyl; $\text{S(O)N(R}^{52})\text{-C}_{1-6}$ alkyl; $\text{S(O)}_2\text{-C}_{1-6}$ alkyl; S(O)-C_{1-6} alkyl; $\text{N(R}^{52})\text{S(O)}_2\text{-C}_{1-6}$ alkyl; and $\text{N(R}^{52})\text{S(O)-C}_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

T^5 is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tetralinyl; and decalinyl; wherein T^5 is optionally substituted with one or more R^{54} , wherein R^{54} is independently selected from the group consisting of halogen; CN; OR^{55} ; oxo ($=\text{O}$), where the ring is at least partially saturated; $\text{N(R}^{55}\text{R}^{56})$; COOR^{55} ; $\text{C(O)N(R}^{55}\text{R}^{56})$; $\text{S(O)}_2\text{N(R}^{55}\text{R}^{56})$; $\text{S(O)N(R}^{55}\text{R}^{56})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $\text{N(R}^{55})\text{-C}_{1-6}$ alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $\text{C(O)N(R}^{55})\text{-C}_{1-6}$ alkyl; $\text{N(R}^{55})\text{-C(O)-C}_{1-6}$ alkyl; $\text{S(O)}_2\text{N(R}^{55})\text{-C}_{1-6}$ alkyl; $\text{S(O)N(R}^{55})\text{-C}_{1-6}$ alkyl; $\text{S(O)}_2\text{-C}_{1-6}$ alkyl; S(O)-C_{1-6} alkyl; $\text{N(R}^{55})\text{S(O)}_2\text{-C}_{1-6}$ alkyl; and $\text{N(R}^{55})\text{S(O)-C}_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

R^{52} , R^{53} , R^{55} , R^{56} , are independently selected from the group consisting of H; and C_{1-6} alkyl.

2. A compound according to claim 1 of formula (Ia)



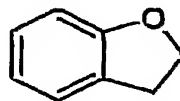
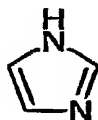
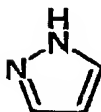
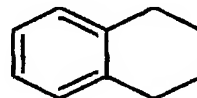
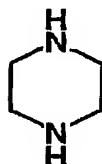
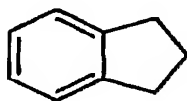
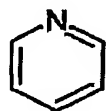
(Ia)

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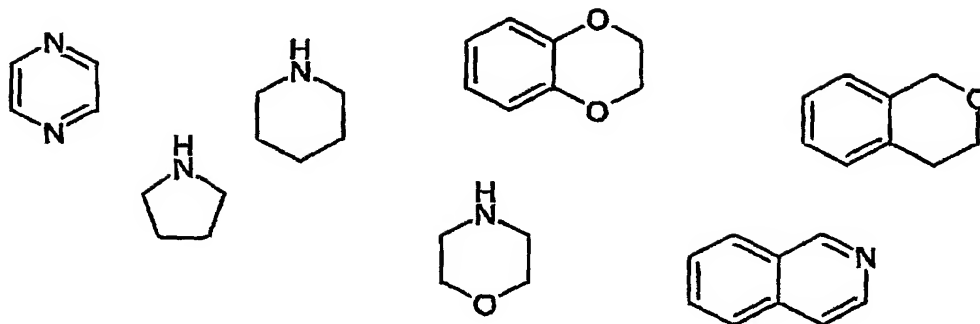
or a pharmaceutically acceptable salt thereof, wherein Z, R¹-R⁷ and X have the meaning as indicated in claim 1.

3. A compound according to claim 1 or 2, wherein Z is phenyl or heterocycle.
4. A compound according to any one of the preceding claims, wherein Z is optionally substituted with 1 or 2 R⁸, which are the same or different.
5. A compound according to any one of the preceding claims, wherein R⁸ is selected from the group consisting of Cl; F; CN; CH₃; and OCH₃.
6. A compound according to any one of the preceding claims, wherein Z is 2-Fluoro-phenyl.
7. A compound according to any one of the preceding claims, wherein R¹, R⁴ are independently selected from the group consisting of H; F; OH; CH₃; and OCH₃.
8. A compound according to any one of the preceding claims, wherein R², R⁵ are independently selected from the group consisting of H; F; and CH₃.
9. A compound according to any one of the preceding claims, wherein R¹, R², R⁴, R⁵ are H.
10. A compound according to any one of the preceding claims, wherein R³ is H.
11. A compound according to any one of the preceding claims, wherein X is C(O).
12. A compound according to any one of the preceding claims, wherein R⁶ is selected from the group consisting of H; and CH₃.
13. A compound according to any one of the preceding claims, wherein X¹ is a covalent bond.
14. A compound according to any one of the preceding claims, wherein m is 0, 1, 2 or 3.
15. A compound according to any one of the preceding claims, wherein R⁷ is Z¹.
16. A compound according to any one of the preceding claims, wherein R⁷ is C₁₋₄ alkyl, substituted with 1-4 R^{29a}, which are the same or different.

17. A compound according to claim 16, wherein R^7 is selected from the group consisting of $CH(R^{29a})_2$; $CHR^{29a}-CH_2R^{29a}$; $CH_2-CH(R^{29a})_2$; $CH_2-CHR^{29a}-CH_2R^{29a}$; and $CH_2-CH_2-CH(R^{29a})_2$.
18. A compound according to any one of the preceding claims, wherein R^{29a} is selected from the group consisting of R^{29b} ; and Z^1 ; and wherein R^{29b} is selected from the group consisting of H; F; Cl; NH_2 ; $NHCH_3$; $N(CH_3)_2$; CH_3 ; and C_2H_5 .
19. A compound according to any one of the preceding claims, wherein R^{29a} is selected from the group consisting of R^{29b} ; and Z^1 ; and wherein Z^1 is selected from the group consisting of T^1 ; and T^2 .
20. A compound according to any one of the preceding claims, wherein T^1 is phenyl; and wherein T^1 is optionally substituted with 1-3 R^{38} , which are the same or different.
21. A compound according to any one of the preceding claims, wherein R^{38} is independently selected from the group consisting of F; Cl; CN; CH_3 ; C_2H_5 ; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3 ; O- CH_3 ; O- C_2H_5 ; S- CH_3 ; SO_2NH_2 ; T^3 ; and O- T^3 .
22. A compound according to any one of the preceding claims, wherein T^2 is selected from the group consisting of



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and wherein T^2 is optionally substituted with 1-2 R^{41} , which are the same or different.

23. A compound according to any one of the preceding claims, wherein R^{41} is selected from the group consisting of OH; CH_3 ; and T^3 ;

24. A compound according to any one of the preceding claims, wherein T^3 is T^4 .

25. A compound according to any one of the preceding claims, wherein T^4 is phenyl, wherein T^4 is optionally substituted with 1-3 R^{51} , which are the same or different.

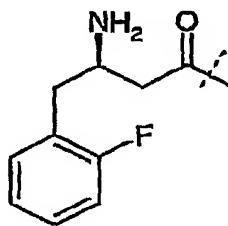
26. A compound according to any one of the preceding claims, wherein R^{51} is independently selected from the group consisting of F; Cl; CH_3 ; C_2H_5 ; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3 ; $O-CH_3$; $O-C_2H_5$; $S-CH_3$; and SO_2NH_2 .

27. A compound according to any one of the preceding claims, wherein T^3 is T^5 .

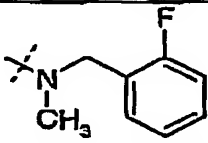
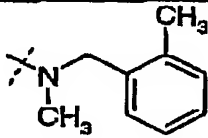
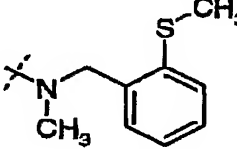
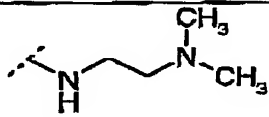
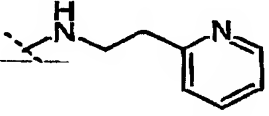
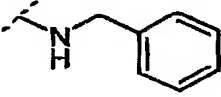
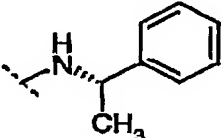
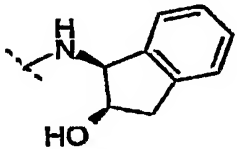
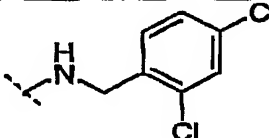
28. A compound according to any one of the preceding claims, wherein T^5 is heterocycle, wherein T^5 is optionally substituted with 1-2 R^{54} , which are the same or different.

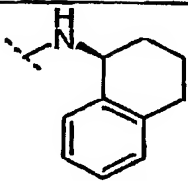
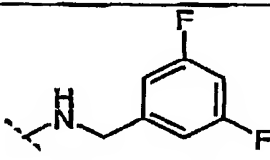
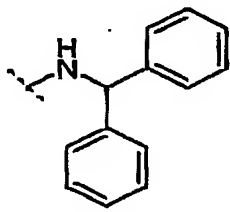
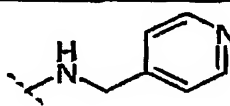
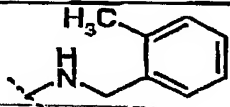
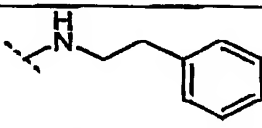
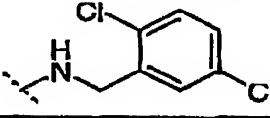
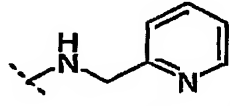
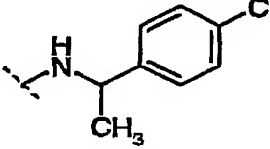
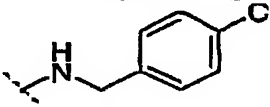
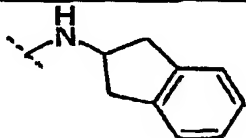
29. A compound according to any one of the preceding claims, wherein R^{54} is selected from the group consisting of OH; and CH_3 .

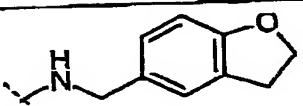
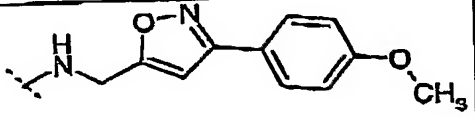
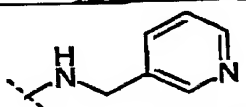
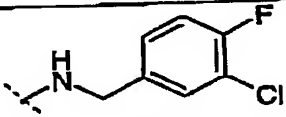
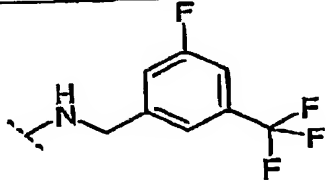
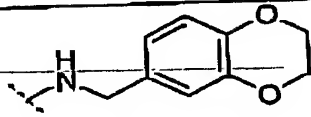
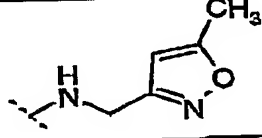
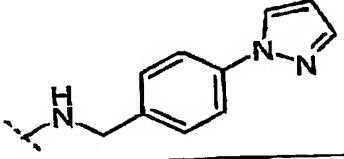
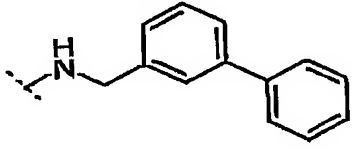
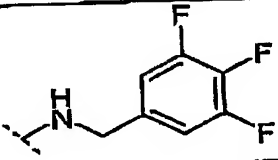
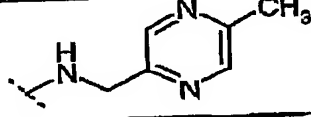
30. A compound according to claim 1 selected from the group consisting of

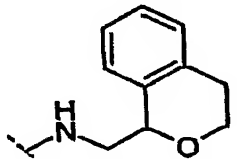
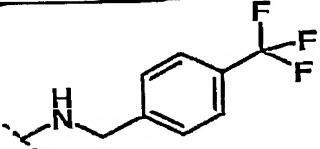
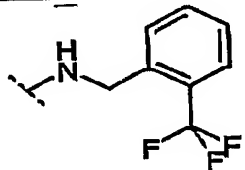
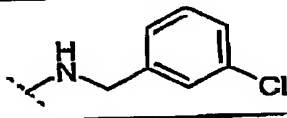
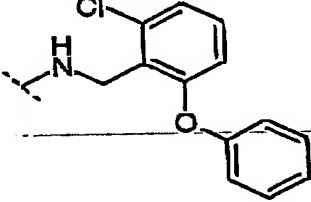
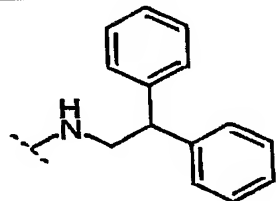
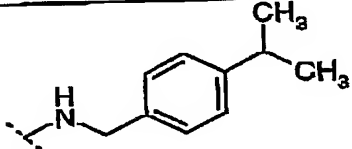
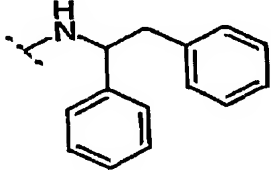


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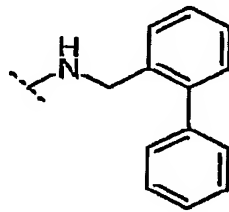
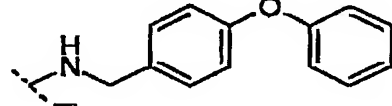
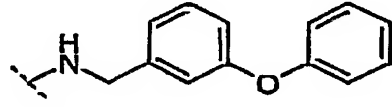
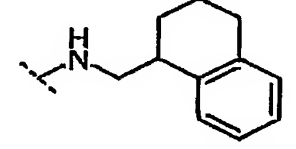
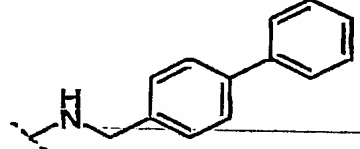
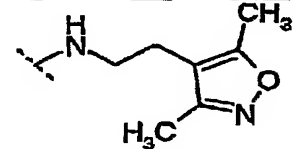
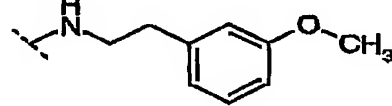
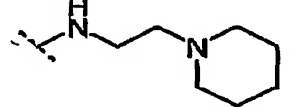
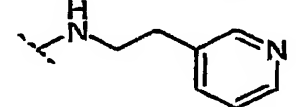
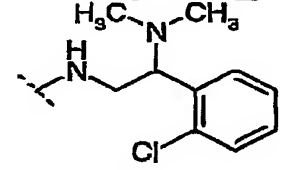
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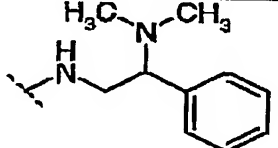
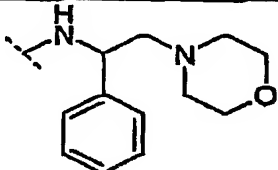
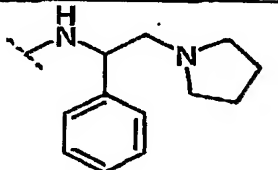
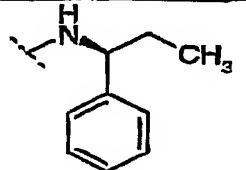
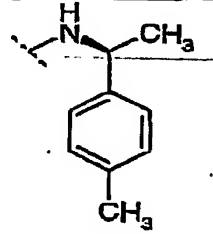
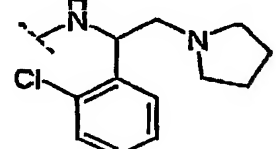
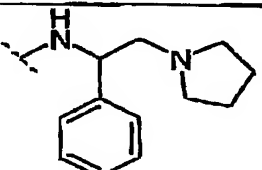
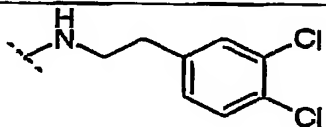
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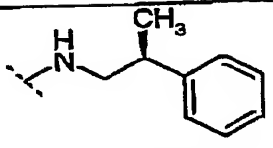
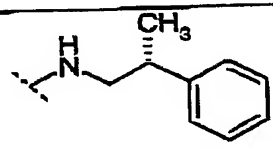
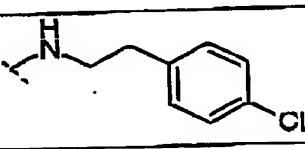
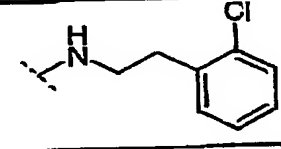
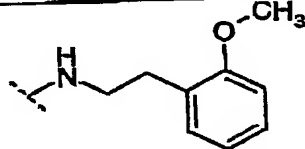
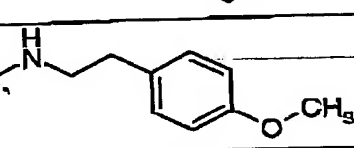
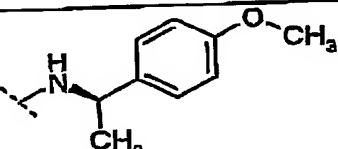
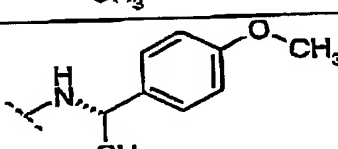
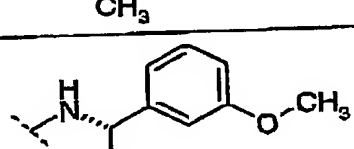
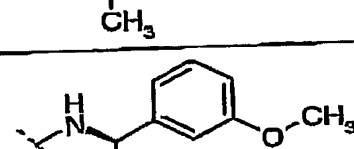
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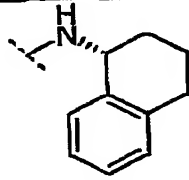
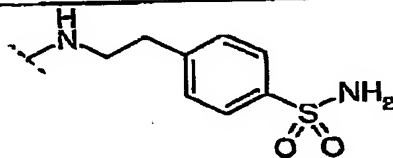
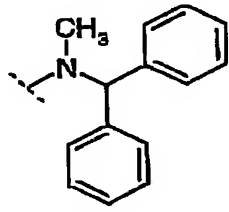
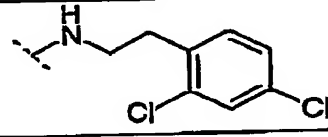
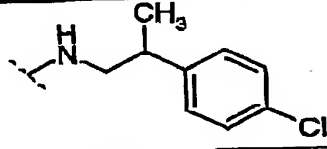
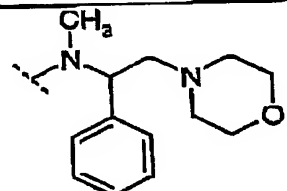
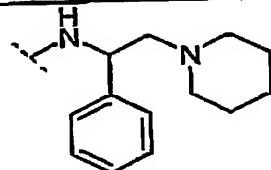
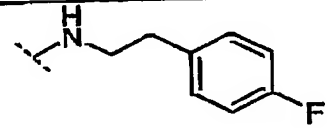
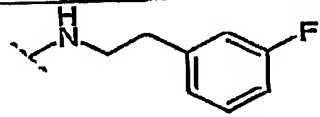
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31. A prodrug compound of a compound according to any one of the claims 1 to 30.

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32. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 31 together with a pharmaceutically acceptable carrier.
33. A pharmaceutical composition according to claim 32, comprising one or more additional compounds or pharmaceutically acceptable salts thereof selected from the group consisting of another compound according to any one of the claims 1 to 27; another DPP-IV inhibitor; insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-1B (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas and other insulin secretagogues; α -glucosidase inhibitors; glucagon receptor antagonists; GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; GIP, GIP mimetics, and GIP receptor agonists; PACAP, PACAP mimetics, and PACAP receptor 3 agonists; cholesterol lowering agents; HMG-CoA reductase inhibitors; sequestrants; nicotinyl alcohol; nicotinic acid or a salt thereof; PPAR α agonists; PPAR α / γ dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPAR α agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; and anti-inflammatory agents.
34. A compound or a pharmaceutically acceptable salt thereof of any one of the claims 1 to 31 for use as a medicament.
35. Use of a compound or a pharmaceutically acceptable salt thereof of any of the claims 1 to 31 for the manufacture of a medicament for the treatment or prophylaxis of non-insulin dependent (Type II) diabetes mellitus; hyperglycemia; obesity; insulin resistance; lipid disorders; dyslipidemia; hyperlipidemia; hypertriglyceridemia; hypercholesterolemia; low HDL; high LDL; atherosclerosis; growth hormone deficiency; diseases related to the immune response; HIV infection; neutropenia; neuronal disorders; tumor metastasis; benign prostatic hypertrophy; gingivitis; hypertension; osteoporosis; diseases related to sperm motility; low glucose tolerance; insulin resistance; its sequelae; vascular restenosis; irritable bowel syndrome; inflammatory bowel disease; including Crohn's disease and ulcerative colitis; other inflammatory conditions; pancreatitis; abdominal obesity; neurodegenerative disease; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type II diabetes; or growth hormone deficiency).
36. Use of a compound according to any one of the claims 1 to 31 as DPP-IV inhibitor.

Abstract

The invention relates to compounds of formula (I)



wherein Z, R¹⁻⁷ and X have the meaning as cited in the description and the claims. Said compounds are useful as DPP-IV inhibitors. The invention also relates to the preparation of such compounds as well as the production and use thereof as medicament.

